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*Harvey, The Man and His Work

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IN the history of medicine there have been many men who have made a single or several great discoveries. There have been numerous men remembered as great lecturers of anatomy. Eminently successful practitioners are present in every community and authorities on embryology have been frequent. Every king of England has had his own physician and the Royal College of Physicians has honoured many men but only one versatile individual has embodied all these achievements. Of such a man I wish to speak this evening. God has been good to many men of history but to Harvey he was bountiful. Harvey was ambitious and his family were financially able to support his ambitions. Harvey was an accurate observer and recorder and he was gifted with the intelligence to correctly interpret what he saw. While Semmelweis and others died without seeing their discoveries generally accepted, Harvey lived for years in the praise of his contemporaries in spite of the fact that his teachings discredited the theories of the old masters.

The life of this man and his work make a study in contrasts. The man in relation to others was one person. Generous, kindly, warm-hearted, giving credit for achievement and excusing mistakes on the part of others, an understanding friend, a sympathetic physician and a student of Aristotle, Galen and Virgil, he was thought of highly and loved by everyone who knew him. The man in relation to his work was another person. Accurate in observation, methodical in recording, accepting everything he saw and little that he read, placing observable facts, and appropriate experimentation above accepted theories, he was the essence of everything that is shrewd and accurate, impartial and reasoning.

William Harvey was born, ironically enough, on April Fool's Day, in 1578, at Folkestone, in the County of Kent, the seventh son of Thomas Harvey. His father was apparently a man of ample means although little is known of him. However, we do know that during the year 1600 he was mayor of Folkestone. We assume that he was a man of keen business sense for during the later years of his life he looked after the various fortunes of his wealthy sons. Very little is known of the early

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life of these seven boys although they probably received their preliminary education in Folkestone. With the exception of William, the Harvey boys journeyed to London and served their apprenticeship as merchants, later becoming merchants dealing principally in goods coming from Turkey.

Having spent several years at King's School, Canterbury, William Harvey was sent by his father to Cambridge. It was probably at Cambridge where he showed his keen interest in Nature and comparative anatomy which led his father to have the boy study medicine. At Cambridge he graduated as a Bachelor of Arts in 1597 and since the best medical teaching of the time was imparted in Italy, Harvey was sent to Padua, a school made famous by Vesalius and Fabricius. Thorough searching of the records of this medical school fail to show any reference to him up until the year 1600 although he must have entered on his studies there in 1598. At Padua each nationality had its representatives on a governing board to control student affairs. Harvey was elected "concilarius" of the English group which, according to history students, entailed being drunk at least forty times a year. However, Harvey became a diligent student, especially in anatomy. This subject was taught by Fabricius in an amphitheatre designed by the teacher himself and lit only by candlelight. Here he gave his classical lectures and here, in the English student, was probably first born the incentive to study the arteries, veins and heart.

Boarding houses at Padua were notoriously unsatisfactory as regards food, warmth and light. The food was scanty, the windows were covered only with linen and artificial light was at a prohibitive price. However, Harvey learned so quickly that he soon drew the attention of Fabricius. They became very close friends. Together they studied the values of the veins, which the older man had previously discovered. Here was the birth of Harvey's interest in the circulation. He would, no doubt, have become a distinguished man, but had it not been for Fabricius and his values of the veins, Harvey might never have written his epical "Circulation of Blood." Fabricius postulated that the valves prevented over-distention of the vessels when the blood passed from the large veins to the small ones and were not needed in the arteries bcause here the blood was always in a state of ebb and flow. It was left to Harvey, doubting the explanations of previous anatomists, and basing his conclusions on observations and experimental facts, to show the true reason for the valves of the veins.

In the year 1602, the University at Padua conferred on Harvey, at the age of 24, the degree of Doctor of Physic. He returned to England and in the same year received the medical degree from the University of Cambridge. He then proceeded to London where he set up practice. He then applied for membership in the College of Physicians. Since only

graduates of English universities were admitted to membership in this important body, we probably have the reason for his qualifying for M.D. at Cambridge.

A few weeks after admission to the College of Physicians, Harvey married Elizabeth Browne, a tall girl of 24 years, dark complexion and somewhat severe aspect. Elizabeth, in all of Harvey's writings, is only mentioned once. The reference is in connection with a pet parrot which the great embryologist thought to be a male but which, on post mortem, turned out to be a female. Mrs. Harvey was the daughter of Dr. Lancelot Browne, physician in turn to Queen Elizabeth and James I. Outside of these few isolated facts, historians are able to tell us little about her.

Having obtained a medical degree, a wife, and a membership in the College of Physicians, Harvey now settled down to practice medicine in London. Patients at first were slow in coming. For this reason he decided to apply for the office of physician to St. Bartholomew's Hospital. This office was held at that time by one Dr. Wilkenson. Applications were received while the physician holding office was still active, the successful candidate being made his assistant. Apparently influential connections were as important then as now, for, having presented recommendation by the king, Harvey was at once appointed to the position. The royal blessing came through one of his brothers who was influential at court.

One year later Dr. Wilkenson died and Harvey took over the full responsibility of physician to St. Bartholomew's Hospital. And so we see him at 32 years of age holding a position of great responsibility, calling forth admiration from his friends and envy from his enemies. His new position gained for him prestige among the profession and the lay people so that his private practice flourished. He attended, while still a young man, many of the distinguished men of the age, among them Lord Chancellor Bacon. In spite of the demands of his position at the hospital and his private practice, he had many hours to himself during these early years. These hours were spent in dissection of many animals as his vast knowledge of vertebrate anatomy proves.

At the age of 37, Harvey was appointed to the office of Lumleian lecturer. The Lumleian lecture was a surgery lecture established by Lord Lumley and Dr. Caldwell at a cost of 40 pounds a year. It was to be continued perpetually for the common benefit of the physicians of London. The reader was to be a Doctor of Physic of good practice and knowledge, and was appointed for life. He was to lecture twice a week throughout the year for one hour, three-quarters of an hour in Latin and the other quarter in English, "wherein that shall be plainly declared for those that understand not Latin." The course of lectures was a definitely outlined set of lectures on surgery and anatomy to cover a six-year period. The course was then repeated.

It so happened that one of the anatomy lectures was to cover the circulation of the blood. Harvey's notes show that he had made his discovery of the circulation of the blood at this time. Although he reported his observations to this group, it was not until 12 years later that he published his findings.

Harvey's fame quickly spread to court and in 1631 Charles I. appointed him Physician in Ordinary. King and physician became very fast friends and remained so through life. At the same time Harvey became family physician to many distinguished families in London. He became a Censor in the College of Physicians, which body ruled over the practicing physicians of London and vicinity. He was now at the height of his career. But the deed that made him immortal was to mar his happiness temporarily. It is said that on publishing his "Exercise on the Motions of the Heart and Blood" his practice fell off considerably. His contemporaries were against him and his patients thought him queer. Fortunately, Harvey lived to see his discovery universally accepted.

From the notes of his Lumleian lectures, we have proof that Harvey believed the blood circulated twelve years before publishing his paper on this subject. Reasons for this are vague. Among his letters we find the following passage:

> " . . . The crowd of foolish scribblers is scarcely less than the swarms of flies in the height of summer, and threatens with their crude and flimsy productions to stifle us as with smoke."

Even in Harvey's day men rushed into print with their newly formed ideas without giving their thoughts a chance to mellow. His book was published by a firm in Frankfurt, Germany. The reason given us the annual book fair held in this town, which gave his work a chance for more rapid spread than if it had been issued in England.

Harvey opens his treatise with a dedication to Charles I. The unadulterated flattery of the dedication is ample proof that Harvey had a great deal of respect for his monarch or that he knew on which side his bread was buttered.

Harvey, then, in orderly and concise fashion describes, in seventeen chapters, the working of the heart and the movement of the blood in a circle. His method of working, comparatively new at the time, was the one which every research worker uses unthinkingly now. He learned what was known already; he formed an hypothesis; and proved it by experiment.

In the introduction there is a brief review of the previous theories on the movement of the heart and the blood. He begins his own discussion with an examination of the living heart. He admits his difficulty

in interpreting the complicated movement but careful observation showed him several basic facts: the heart was composed of muscle; this muscle contracted similarly to the biceps muscle; that the systole was more important than the diastole. These facts he was able to observe, especially in cold-blooded animals or warm-blooded animals in whom the heart had begun to fag. If the ventricle were pierced, the blood gushed out of the hole at each systole.

Having dealt with the heart in broad terms, he turns his attention to the arteries. He shows that the pulsation of the arteries is dependent on the action of the heart and that blood is forced into them by the systole of the left ventricle and not sucked into them by active dilation. Section of a living artery, he said, will show a spurt of blood occurring simultaneously with each systole of the left ventricle.

The author then proceeds to describe the action of the heart in more detail. He says:

> "First of all, the auricle contracts and in the course of its contraction forces the blood (which it contains of ample quantity as the head of the veins, the storehouse and cistern of the blood) into the ventricle which, being filled, the heart raises itself straightway, makes all its fibres tense, contracts the ventricles and performs a beat, by which beat it immediately sends the blood supplied to it by the auricle into the arteries. The right ventricle sends its charge into the lungs by the vessel which is called the vena arteriosa (pulmonary artery), but which in structure and function and all other respects is an artery. The left ventricle sends its charge into the aorta and through this by the arteries to the body at large.
>
> "These two movements, one of the ventricles, the other of the auricles, take place consecutively, but in such a manner that there is a kind of harmony or rhythm preserved between them, the two concurring in such wise that but one movement is apparent, especially in the warmer blooded animals in which the movements in question are rapid. Nor is this for any other reason than it is in a piece of machinery in which, though one wheel gives movement to another, yet all the wheels seem to move simultaneously; or in that mechanical contrivance which is adapted to firearms, where the trigger being touched, down comes the flint, strikes against the wheel, produces a spark which, falling among the powder, ignites it, upon which the flame extends, enters the barrel, causes the explosion, propels the ball, and the mark is attained—all of which incidents by reason of the celerity with which they happen seem to take place in the twinkling of an eye . . . Even so does it come to pass with the movements and action of the heart."

Up to this point the writer has proven his statements by experiments or direct observations. Having shown that the blood moves in a circle, he is somewhat at a loss to explain its movement through the lungs. That the blood is carried there by the pulmonary artery and returned to the heart by the pulmonary veins, he is sure. About the passage from arteries to veins he is able only to speculate. He suggests that the blood percolates the parenchyma of the lungs. This was probably the closest any investigator could have come to the truth in Harvey's time since the microscope was not invented until the latter part of the seventeenth century.

Throughout his paper, Harvey attempts to keep away from discussion on the functions of the blood as much as possible. Many wild speculations on this subject had been made by previous writers confusing the issue with such terms as spirits, vapours, and inherent heat. As soon as Harvey enters this field he immediately becomes involved in error. He says:

> "It must be because the larger and more perfect animals are warmer, and when adult their heat greater, ignited I might say, and requiring to be damped or mitigated, that the blood is sent through the lungs in order that it may be tempered by the air that is inspired, and prevented from boiling up and so becoming extinguished or something else of the sort."

We must not criticize him too severely for this mistake for at that time it was believed that the arteries cooled the blood and the lungs cooled the heart. At least Harvey was closer to the truth.

The main part of the treatise is that the blood circulates, as explained before. To prove this point he makes three propositions which, being proved, prove the main point:

> "First, that the blood is incessantly transmitted by the action of the heart from the vena cava through the lungs to the arteries.
>
> "Secondly, that the blood under the influence of the arterial pulse enters and is impelled in a continuous, equable, and incessant stream through every part and member of the body, in much larger quantity than is sufficient for nutrition or than the whole mass of fluids could supply.
>
> "Thirdly, that the veins return this blood incessantly to the heart.
>
> "These points being proved, I conceive it will be manifest that the blood circulates, revolves, is propelled, and then returning from the heart to the extremities, from the extremities to the heart, and thus that it performs a kind of circular movement."

Through seventeen chapters the author proceeds to prove his three points by argument, experimental facts and by known clinical facts. His arguments are logical, his experiments are simple and conclusive, and the clinical facts mentioned are those observed but their significance missed by all men.

After exhausting the subject, in the fourteenth chapter he concludes:

> "And now I may be allowed to give in brief my view of the circulation of the blood, and to propose it for general adoption.
>
> "Since all things, both argument and ocular demonstration show that the blood passes through the lungs and heart by the force of the ventricles, and is sent for distribution to all parts of the body, where it makes its way into the veins and pores of the flesh, and then flows by the veins from the circumference on every side to the centre from the lesser to the greater veins, and is by them finally discharged into the vena cava and right auricle of the heart, and this in such quantity or in such afflux and reflux, thither by the arteries, hither by the veins, as cannot possibly be supplied by the ingesta, and is much greater than can be required for mere purpose of nutrition; it is absolutely necessary to conclude that the blood in the animal body is impelled in a circle, and is in a state of ceaseless movement; that this is the act or function which the heart performs by means of its pulse, and that it is the sole and only end of the movement and contraction of the heart."

From the time of publishing his paper until his retirement, Harvey spent most of his time in personal attendance on his king. Since much of this time was spent at war with Scottish barons, Harvey made several trips into Scotland with the king. No sooner had the trouble in Scotland been settled than civil war broke out in England. The parliament and the king fought bitterly. In spite of the fact that Harvey had been ordered by the parliament to attend the person of the king he was suspected of being a vehement Royalist, probably rightly so. A mob of citizen-soldiers broke into his home, took or destroyed many valuable museum specimens and scattered important papers. Finally the king set up his court at Oxford and here Harvey spent several years of comparative peace. Here he was able to engage again in the things he most loved: animal observation and experimentation. In 1645 he was elected Warden of Merton College, one of the colleges of Oxford. He held this position for only one year, until the surrender of Oxford to parliament.

Harvey was then 68 years old. He suffered from gout. Three of his brothers died within two years. His wife must have died at this time also. His political party had been defeated and his king was to be beheaded. Harvey was thus in no mood to return to private practice. He was more than a welcome guest at the homes of his surviving brothers and so spent most of his days with them. His gout bothered him considerably. He had a cure for it of his own invention which was rather unique. Aubrey says:

> "He was much and often troubled with the gout, and his way of cure was thus: He would sit with his legs bare, though it were frost, on the leads of Cockaine House, put them into a pail of water till he was almost dead with cold, then betake himself to his stove, and so 'twas gone."

Harvey's last big literary effort was his essay on "Development." Throughout his professional career he had been interested in development and had written voluminous notes on the subject. He might never have published any of his findings on this subject had not a friend prevailed on him until he gave him his notes to publish.

His letters to the continent show that his mind was active up until his death. In retirement at the house of his brother Eliab he spent many hours with his animals and his books. On June 3, 1657, William Harvey woke with a paralyzed tongue. He made signs to his apothecary to bleed him in the tongue. This procedure did little or no good and towards evening of the same day he passed away, probably from a cerebral hemorrhage.

His body was taken to London where it remained until June 26, a period of 23 days, at which time it was removed in state to Hempstead, a small village fifty miles from London. Here his brother Eliab had

built, two years previously, the Harvey Chapel, beneath which he had built a vault to bury the members of his family. The body was laid to rest coffinless, merely wrapped in a shell of lead, as was the Harvey custom. The lead shell, first placed in the vault below the Chapel, became weather-beaten and was later moved by members of the College of Physicians to the Chapel above, where it still rests.

There are those who would attempt to discredit Harvey's work. Some claim that the circulation had been discovered previous to Harvey. Some claim that the discovery was long overdue, that the ground work had been laid and that all the Englishman had to do was to put the pieces together. Dower and Willis, the two most authoritative historians on Harvey, agree that he did first discover the circulation beyond a doubt, and that his work was completely original. He was the first of the modern physiologists since he was the first to perceive the relations between the lowest and highest of animals. He thus used the simplicity of structure and of function of the one to explain the complexity of structure and function of the other. He began a completely new era in which experimental proof took the place of complicated theories from authoritative sources. Thus we honor him, not only for the greatest discovery in medicine but as the originator of the truly scientific spirit.

Diaphragmatic Hernia

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IN the presence of atypical symptoms referable to the upper abdomen or thorax, diaphragmatic hernia must be given serious consideration in the differential diagnosis. Before the age of radiology, Leichbenstein had collected 252 cases, Lacher 276 and Grossier about 500 cases. These were discovered usually during operations or necropsies. With the advancement of X-ray diagnostic methods diaphragmatic hernia has been found much more frequently and several thousands of cases have been reported, mostly following routine examinations of the stomach.

Classification: By diaphragmatic hernia is understood any escape of the organs, normally lying below the diaphragm, through the diaphragm into the chest cavity, whether the escaped organs are enclosed in a true hernial sac or not. A protrusion of the abdominal viscera may take place through a wound or through a portion of the diaphragm that is deficient.

For the purpose of clarifying the classification of diaphragmatic hernia it will be necessary to include certain conditions which are not true herniae.

Diaphragmatic herniae are congenital or acquired:

I. Congenital: (1) Herniation of stomach, (2) Herniation of other organs, (3) Congenital absence of the diaphragm.
II. Traumatic (acquired).

I.—CONGENITAL HERNIAE

Congenital herniae are due to an arrest of foetal development and occurs usually on the left side, since congenital defects of the diaphragm are more frequent on that side, and the muscle congenitally deficient is protected on the right side by the liver. The opening is more frequently in the muscular than in the tendinous structure and more often in its posterior portion.

The places where the muscular fibres of the diaphragm are normally deficient are at the "pleuro-peritoneal hiatus"—also called Bochdalek foramen—occurring on either side of the lateral portion of the external arched ligament, which is a common site for hernia in children. The other place is the Foramen of Morgagni between the costal and sternal attachments. A hernia may occur through the œsophageal opening. Finally, there may be a congenital defect in the diaphragm. The size

of the aperture varies from a small hole to one involving one-half of the diaphragm. Often these defects are associated with other congenital defects.

These herniae are classed as true when the peritoneal sac is present and as false when the viscera lie free in the plural cavity. The latter form is more common.

1. *Herniation of stomach:* Herniation of stomach may be considered under three different headings, *viz:* (a) Thoracic stomach, (b) Short oesophagus causing part of the stomach to remain above the diaphragm, (c) Hiatus hernia or a true herniation of stomach, where the oesophagus is of normal length, and may or may not take part in the hernia. The first two in the true sense are not herniae, since the displaced organs have never been in the abdominal cavity, but have always been either entirely or partly in the thorax. They are, however, commonly considered as herniae and hence are classified as such for practical purposes.

(a) Thoracic stomach, named by Bailey in 1919, is a rare condition. When this occurs, the œsophagus is usually very short and the stomach may be entirely within the thorax. In some, a portion of the distal end of the stomach will remain below the level of the diaphragm. The stomach may be surrounded by a serous sac which communicates with the peritoneal cavity and, as a rule, is the only organ involved in the abnormal position.

(b) Congenitally short oesophagus, which generally terminates a short distance above the diaphragm, causes a part of the cardiac end of the stomach to remain above the diaphragm. The oesophagus ends at the seventh or eighth thoracic vertebra.

(c) Hiatus hernia, or true herniation of the stomach through the oesophageal hiatus, is perhaps encountered more commonly than any other. The oesophageal hiatus is a muscular one and it is conceivable that there occurs some relaxation of the ring as the age periods are more advanced. There is some congenital defect in this ring, which may not show until late. It is interesting to note that it occurs in the higher age group with maximal occurrence at 51, and it appears to be slightly more common in the female sex.

In this hernia the oesophagus may remain fixed below the diaphragm and does not form a part of the hernia—the so-called para-oesophageal hernia—or the oesophagus may form a part of the hernia.

It is very important to differentiate herniae of the two last groups, because a hernia with congenitally short oesophagus cannot be treated surgically, due to the shortness of the oesophagus and the impossibility of placing all of the stomach within the abdominal cavity. On the other

hand, a true hernia of stomach is amenable to surgical treatment. Radiological examination is the best way to differentiate these types. One of the characteristic features on X-ray of the true hernia group is the rounded contour of the herniated part of the pars cardiaca. This is quite different from the contour seen in the short oesophagus group in which the superior portion of the pars cardiaca is generally pointed, and the oesophagus empties into this upper or peaked portion. In the true hernia the distal end of the oesophagus enters the stomach in its normal position. The supine position is employed in the examination of diaphragmatic lesion, and careful observations should be made with the fluoroscope during the swallowing of the opaque meal.

In considering the aetiology of this group of herniae, only the congenital variety was mentioned. There are, however, other theories as to the origin of congenital short oesophagus and thoracic stomach.

(1) The enlarged oesophageal hiatus or any other congenital aperture in the diaphragm occurs as a result of embryologic failure of fusion. This may not be the result of an inhibition in the development during the embryonic period, but rather the result of a dissociation of the embryonal aggregation of cells that later form the diaphragm.

(2) Almost invariably thoracic stomach is the result of herniation through a congenital hiatus hernia and may occur at any time after birth. Einhor reports a case where the aetiological factor was trauma (the lifting of a barrel).

(3) The short oesophagus is the result of cessation of traction on it by the stomach, which has assumed a position in the thorax. In many instances a short oesophagus is the result of inflammatory changes at its lower end.

2. *Herniation of other organs:* It is in this group of congenital herniae that we find the greatest departure from the normal, as well as variation in the organs involved and variation in the site of herniation. They are most commonly found in infants and children. Their symptomatology is often related more closely to the respiratory system than to the alimentary tract. The great majority of these herniae are found on the left side and occur through a persistent hiatus pleuroperitonealis or foramen of Bochdalek. Less commonly the hernia occurs through the parasternal foramen of Morgagni. Occasionally, it may occur through defects in other parts of the dome of the diaphragm. In this variety of hernia, organs other than the stomach are generally involved, both the small and large intestine, omentum, spleen, and the left lobe of the liver. Early death is the rule in these cases, due either to asphyxia or intestinal obstruction.

3. *Congenital absence of diaphragm* is a rare condition which may be associated with other congenital anomalies such as absence of the

lung on the affected side. Generally the patient with this condition succumbs early although cases have been reported in which they have reached adult life and, strangely enough, had very few symptoms.

II.—TRAUMATIC OR ACQUIRED HERNIAE

Trauma is thought by some observers to be responsible for one-third of all diaphragmatic herniae. These may occur in children or adults and are always false. Hedblour found that approximately 90 per cent occurred in males and that about 50 per cent were due to penetrating injuries. Of those due to non-penetrating injuries only 23 per cent were due to crushing, and 36 per cent were due to falls. Traumatic hernia may occur through any part of the diaphragm, but 95 per cent are found on the left side. The actual lesion is a tear in the diaphragm which usually runs radially from the central tendon and may extend from the dome to the periphery. The initial injury may be relatively small, as from a bullet wound, but gradual enlargement of the opening is the rule. The herniated parts may be any portion of the gastro-intestinal tract and associated organs.

Eventration of the diaphragm, while not a hernia, may resemble one and must be considered in the differential diagnosis. This unusual condition may be defined as a marked protrusion of one dome of an intact diaphragm into the thoracic cavity. The aetiology of this condition is unknown, but the consensus of opinion is that it is probably congenital. The diagnosis is made by fluoroscopic examination with an opaque medium in the stomach. The hemi-diaphragm on the affected side remains stationary, whereas the other half moves normally.

SYMPTOMATOLOGY

The symptoms of diaphragmatic hernia may be cardiac, respiratory and gastro-intestinal. In a single case, the symptoms may be attributed to all these systems, but it is usual for those from one system to predominate.

In cases in which there is dysphagia, the clinician's attention is directed early toward the oesphagus, and he is apt to think of cardiospasm or carcinoma of the oesophagus, requesting X-ray examinations with these lesions in mind. Dysphagia occurs chiefly in the herniae with a short oesophagus but it also may be present with other types. The dysphagia is usually the intermittent, not the progressive type seen with carcinoma of the oesophagus, and frequently it occurs only at the end of a heavy meal. Patients observe that they do not have symptoms if they eat a "light diet." Relief from dysphagia follows vomiting.

Patients with diaphragmatic hernia frequently have symptoms that stimulate peptic ulcer or the hyperacidity syndrome. The most promi-

nent clinical features are epigastric distress, pain, or cramps occurring one-half to one hour after meals and made worse by food and relieved by vomiting. Relief may also be obtained by a bowel movement, passing flatus, belching, or taking an enema; these measures tending to change the intra-abdominal pressure. The symptoms may occur intermittently, they may be present after only one meal such as the evening meal which is usually the heaviest, or they may be present only when the patient eats before retiring.

Diaphragmatic hernia at times causes symptoms which suggest chronic gall-bladder diseases. The patient complains of pain in the upper right quadrant radiating at times to the epigastrium or to the back. The attacks are associated with heavy meals. Nausea and vomiting may follow later, usually relieving the discomfort. The distinguishing feature is the fact that with diaphragmatic hernia simulating cholecystitis there is usually no residual tenderness in the upper right quadrant after the pain passes. Cholecystography shows normal findings, and the X-ray studies of the gastro-intestinal tract reveal the hiatus hernia.

Difficulty in breathing immediately after birth should always suggest the possibility of a defect in the diaphragm. This symptom may moderate after a few days only to reappear in a few weeks or months. There will usually also be difficulty in feeding, and failure to gain weight normally. The chief physical signs are small abdomen displacement of heart and absence of breath sounds over the affected side.

Symptoms of cardiorespiratory disease must be distinguished carefully from those produced by diaphragmatic hiatus hernia. The patient may complain of symptoms which very closely simulate angina pectoris. There may be pain beginning in the praecordium or in the epigastrium and radiating to the left shoulder or down the left arm. The trouble usually proceeds from the stomach, as from pressure under sternum, frequent regurgitation or heartburn; or it is a question of oppressive tension in the lowest part of the oesophagus and in the first part of the stomach whereby the vagus nerve is irritated. After many recurrences of the attacks the musculature is damaged on account of the decrease of blood in the coronary vessels. To distinguish these cases from those of true angina pectoris, the relationship of the pain to exertion, the electro-cardiographic tracings and X-ray of the stomach and oesophagus must be carefully evaluated. Both may be present together.

Some patients complain of pain in the region of the ensiform cartilage, severe dyspnoea and cyanosis while eating or shortly after eating. Frequently these patients get relief by deep breathing, stretching, etc. Some will note that the relief is synchronous with the sensa-

tion of passage of food from the thoracic to the abdominal portion of stomach.

Strangulation or complete obstruction of the hernia may occur. The symptoms of these complications are sudden severe pain in the left upper epigastrium which is only slightly relieved by morphine. Severe and persistent vomiting soon ensue. Physical examination reveals rigidity of the upper part of the abdomen.

Many cases of diaphragmatic hernia are asymptomatic, but this must not, when present, deter the physician from a thorough investigation of remainder of the gastro-intestinal tract. Symptomless diaphragmatic hernia may be associated with any other disease of the gastro-intestinal tract such as diverticulosis of the colon, diverticulum of the duodeum, etc.

Physical Signs: Most of the herniae do not have any evident physical signs. Only the large hiatus hernia may demonstrate some, such as asymmetry of the chest. The ribs are usually more widely separated, with or without a flare of the costal margin, on the affected side. Palpation usually does not help. Percussion may reveal a tympanitic note which may be limited to the base of the lung or may be elicited higher toward the axilla. Shifting the position of the patient may cause a marked change in the note. Percussion may also reveal failure of the left diaphragm to descend. On auscultation of the chest, a high pitched tinkling sound may be heard or gurgling and splashing sounds may be audible.

DIAGNOSIS

The diagnosis of diaphragmatic hernia is almost entirely dependent upon the radiological examination. The existence of the condition may be suspected from a film of the chest, but for accurate diagnosis it is necessary to employ opaque meal and both the fluoroscopic and roengenographic techniques. Particular attention should be devoted to determine the length and position of the oesophagus, as this may determine the treatment.

The presence of diaphragmatic hernia may be confirmed or noted at the time of laparotomy by palpating the oesophageal openings in the diaphragm. The type of hernia cannot be determined by this method.

Physical examination alone is not of great value in the diagnosis of this condition. While large herniae may be found to be present by physical findings, the majority of cases would be missed, since by far the greater number of herniae are small or of only moderate size. The history is often suggestive of such a condition, but it usually simulates other pathological conditions such as ulcer or gall-bladder disease. Hence, to make a diagnosis from the history alone would be quite hazardous.

TREATMENT

The treatment of diaphragmatic herniae can be divided into medical and surgical. Not all herniae can be treated surgically. Those are the ones where there is a short oesophagus.

In the medical management of patients with diaphragmatic hernia, the patient should be instructed to eat small meals frequently and to maintain an erect posture for a period of several hours after meals. It is inadvisable for the patient to eat before retiring at night and even with those precautions, some patients will find it more comfortable to sleep in a semi-cumbent position.

If the gastro-intestinal symptoms are not sufficiently relieved following medical management or if there are frequent and severe attacks of cardio-respiratory symptoms, or if there is danger of obstruction or strangulation, surgery is indicated. Operative replacement of the herniated viscera and repair of the abnormal opening in the diaphragm is the only treatment that insures complete relief from the symptoms. The hernial opening is best repaired through an abdominal approach, though some prefer thoracic. The abnormal opening is closed with fascia lata and interrupted linen sutures. Temporary or permanent interruption of the phrenic nerve is of value as a preliminary procedure to radical closure of large openings, and is particularly useful when there is deficiency or loss of structure of the diaphragm. There is always a high percentage of recurrence.

CONCLUSION

1. Diaphragmatic hernia is recognized more frequently than formerly. Average age incidence 51 years.

2. It does not produce any characteristic clinical picture. Most important symptom is dysphagia, and symptoms simulating gall-bladder disease, cardio-respiratory disease or hyperacidity syndrome.

3. Most of the diaphragmatic herniae are incidental findings on X-ray and are symptomless.

4. Positive diagnosis of this condition is possible only by radiological examination.

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Thrombophlebitis

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Introduction.—Although not an everyday complication of operative procedures, thrombophlebitis still remains sufficiently common to harass the already overtaxed profession. Occurring in 0.6 per cent of all surgical convalescents, as an unexpected sequel to an otherwise successful operation it warrants all efforts expended by Ochsner, DeBakey, Homans, Best and Murray to prevent it. These men and many others have rationalized our present concepts of thrombophlebitis and have prepared the way for intelligent prophylaxis and therapy.

* * *

Clinical Classification.

THROMBOPHLEBITIS usually attacks persons who have been confined to bed because of surgical operation, childbirth, injury or disabling disease. This is what Homans calls the "thrombophlebitis of hospitalization." There are several varieties of the process differing in anatomical site, clinical manifestations and prognostic significance; they are classified as follows:

1. Femoro-iliac thrombophlebitis,
2. Thrombo-phlebitis in prostatic and uterine veins,
3. Thrombo-phlebitis in deep veins of the lower leg,
4. Thrombo-phlebitis in superficial veins,
5. Thrombo-phlebitis in varicose veins,
6. Thrombo-phlebitis of the axillary vein.

1. Femoro-iliac thrombophlebitis

Synonyms: Milk leg, Phlegmasia Alba Dolens.—The site of this condition is the upper femoral and external iliac veins. Its greatest incidence is following operation or injury in individuals over 50 years of age. The precipitating factors are extremely variable. It is more likely to follow labour or pelvic operations but is also often associated with acute fevers; with circulatory failures; with debility; and with fractures of the lower limb.

Symptoms: The disease begins in one of two ways: (1) It may have an insidious onset with no oedema. (2) It may be acute; with swelling so tense that in 72 hours the limb will not put on pressure. Pain may be a feature. When present, it is usually referred to the groin, inner thigh or back of the calf, and varies in severity from a feeling of slight soreness to very agonizing cramp-like pains.

Signs: A slight rise in temperature and pulse rate is usually the

first sign; followed in 24 hours by the pain and in 48 hours by the oedema.

Oedema, when present, starts in the ankle and mounts rapidly to involve the entire leg. There is no cyamosis, the leg appearing pasty white.

The arterial pulse is weakened or may disappear in the peripheral vessels and even in the femoral. This is due to the reflexly excited arterial spasm that may be severe enough to cause gangrene, and confuse the diagnosis with arterial embolism. The temperature of the leg is unchanged and there are no lymphatic streaks.

The course of a thrombophlebitic process is very variable. In a mild case there is moderate swelling which disappears in about ten days and leaves no residual oedema.

A severe case rapidly develops an extreme degree of brawny swelling and there may be no change in the leg for months. When the swelling does subside it usually does not do so completely, so that the affected limb remains larger throughout life. In addition, it remains subject to oedema, and even to recurrences of the acute process. In some, the thrombophlebitis passes from one leg to the other, recurring later in the one first attacked.

Sequelae: The venous circulation remains surprisingly adequate, the deep veins of the lower leg seldom being involved and a good collateral circulation being easily established. Some large veins may be left superficially which, in time, become varicose. Oedema of the ankle may remain, but there is no cyanosis after recovery. The main difficulty is in the superficial tissues which may later develop post-phlebitic induration and ulceration, regardless of whether the acute attack left them oedematous. This complication appears as areas of oedema redness, pigmentation and ulceration.

2. Thrombophlebitis in the Prostatic and Uterine veins

This condition may be found at autopsy to be the source of a fatal pulmonary embolism, but it cannot be diagnosed clinically, and so need not concern us here.

3. Thrombophlebitis in the Deep Veins of the Lower Leg

This differs from the Femoro-iliac variety in that it usually occurs during active life from some trivial cause as a minor injury below the knee, a sprain or a fracture of one of the bones of the foot. It may also be a complication of a respiratory or rheumatic infection.

The process occurs in one or several groups of deep veins in and among the great, flat muscles of the calf. The leading symptom is a slight lameness on forced dorsiflexion of the foot or in putting weight on the toes as in walking up stairs.

The only signs may be a slight swelling of the ankle and a cyanotic tinge to the foot. There is no tenderness in the calf, even on deep pressure.

The diagnosis may be confirmed by the following sign which Homans considers to be pathognomonic: discomfort is felt at the back of the upper calf and knee with some limitation of passive motion when the tendo Achilles is put upon the stretch.

A few days in bed will usually clear up the local signs and symptoms, but should the patient go about again the initial soreness and swelling will return. If the rest and exercise cycle be repeated the chances of pulmonary embolism become greater, because under these conditions a long propagating thrombus is most apt to form.

4. Thrombophlebitis in Superficial veins

(a) *Phlebitis migrains.*—This is often an accompaniment of Buerger's disease, but it may occur without any obvious cause. The course is both interesting and exasperating. A one or two-inch stretch of a superficial vein on the lower leg becomes solid, thickened and slightly tender for a week or two, and then, also without apparent reason, softens and returns to normal. However, now another area, proximal to the first, is similarly affected. The cycle may be repeated many times, and no form of treatment seems to have much effect on the course. There is usually a tendency to recurrence throughout life.

(b) *Superficial Thrombophlebitis—non-migrating.*—As a result of local chafing, severe coughing or exposure to unusual cold the disease may suddenly appear in locally dilated veins. It may heal without any clinical evidences ever being present and, especially in adipose women, its diagnosis from a mild cellulitis is difficult. The importance of superficial thrombophlebitis lies in the fact that it tends to be chronic, and may extend at any time into the great saphenous vein and there give off an embolus.

5. Thrombophlebitis in varicose veins

Varicose veins have fibrosed, unhealthy walls, and this, associated with the slow current through them, makes them a very favourable site for thrombosis. However, although the thrombosis may spread widely through the varicose system, there is practically no danger of embolism because the thrombus attaches more solidly to an unhealthy vein wall, and, if it does reach to the saphenous opening, it halts there as it encounters the strong blood stream in the femoral vein. Furthermore, although the tissues immediately surrounding the affected veins may become inflamed, there is no diffuse invasion of the fat and deep fascia. Thus the importance of this condition lies, not in its dangers, but in the fact that, once thrombosed, a varix is very susceptible to a recurrence.

Usually the process begins in a sacculation just below or above the knee, and then spreads up and down the leg. Once half-way up the thigh it commonly extends to the saphenous opening. The thrombosed vein now stands out as a solid, tortuous cord. There is some redress of the overlying skin, tenderness, local oedema and induration. Little change is seen over a period of several weeks, after which there is softening and organization of the thrombus, the lumen of the vessel is restored and the vein seems little altered from its condition before the onset of the phlebitis. In rare cases, when the infection is very active, an abscess may form, but this is unusual and probably due to some associated cause.

6. Thrombosis of the axillary vein—effort thrombosis

This condition is rare. It is almost always associated with some unaccustomed effort made with the arm elevated. There is a history of strained exertion followed almost at once by pain and swelling of the arm. Within a day or two the arm is blue and oedematous, but there is no sign of local active infection. The superficial veins become prominent, and the axillary vein is felt as a solid cord which may be tender.

With proper care the condition clears up in ten to fourteen days. There are no permanent after-effects but residual weakness, oedema and stiffness may prolong convalescence. Embolism is not a danger. Rarely, a persistent causalgia-like state will complicate the disease.

Pathology and pathogenesis

A consideration of the mechanics of intravascular clotting is integral to an understanding of thrombophlebitis.

When the endothelium of a vein is damaged or the blood stream slowed below a critical velocity platelets accumulate at injured or predilected areas and adhere to the vessel wall. Here they form the basis of an intravascular clot. The platelets are soon covered with layers of leucocytes. The latter have a lighter specific gravity than the erythrocytes and travel marginally in the current. The initial slightly projecting platelet thrombus interferes with the smooth progress of the blood stream, causing many eddies. Whirling in these eddies, the white blood cells contact the platelet projection and attach to it. The white thrombus has been formed. On it are superimposed red blood cells, white blood cells and fibrin (released when injured platelets enzyme acts on serum fibrinogen). The extended clot is mixed, both white and red. To it is added the red clot which is similar to a post mortem clot. Instead of a localized area of thrombosis, we may see a thrombus 10 to 12 inches long, not entirely occluding the vessel, but suspended in the passing blood stream. It is liable at any moment to be carried away by the flow in part, or as a massive embolus.

Technically, a thrombus which starts as a laying down of a white clot and is extended out into the blood stream by the addition of red clot is called a propagating thrombus. How far it extends depends chiefly on the length of blood vessel present that has a slow flow. As soon as the propagating thrombus reaches a speedy current it stops. An oft quoted example of this sudden curtailment of thrombus extension is the invariable cessation of thrombosis in the long saphenous vein at its junction with the femoral vein. In the latter the speed of the circulation is usually sufficiently rapid to prevent further propagation. It is thought that the rapid stream maintains the formed blood elements in the central current, their velocity being too great for them to drop out and adhere to the red thrombus. The usual extension of a thrombus arising in one of the deep calf veins is indeterminable. It may and often does reach the femoral vein. Thrombosis of the femoral vein passes into the external iliac and possibly the common iliac, finally involving the inferior vena cava. Because this propagating thrombus is so long, so loosely attached, and only incompletely occluding the vessel lumen, there is great possibility of embolization. The downward growth of a femoral vein thrombus cannot be prognosticated, for it is variable in every case.

Now that we recognize the more obvious mechanics of intravenous clotting let us review the causes predisposing to venous thrombosis with particular reference to thrombophlebitis. Thrombosis is found in vessels whose walls are injured or in which the blood stream is very much slowed. We have outlined the facts that lead to thrombosis under these two headings:

Possible causes of predispositions to thrombosis—in thrombophlebitis:

1. *Injured vessel wall endothelium:*
   (a) infection
      1. intravascular—bacteria in the blood stream originally,
      2. perivascular—bacteria in tissue fluids as a result of a lymphangitis;
   (b) trauma—mechanical laceration of endothelium by fracture, surgical manipulation, etc.;
   (c) endothelial allergy to products resulting from trauma of surrounding tissues.

2. *Slowing of circulation:*
   (a) anatomical
      1. the pressure of the right common iliac artery on the left common iliac vein at the level of origin of the hypogastric artery;
      2. tension of the inguinal ligament on femoral vein;

(b) poor venous return
   1. muscular inactivity accompanying rest in bed;
   2. shallow thoracic breathing—leads to thoracic congestion;
   3. pelvic congestion
      (a) in pregnancy and puerperium,
      (b) intra peritoneal or intra abdominal tumours,
      (c) postoperative distension,
      (d) obesity,
      (e) failing heart;

(c) dehydration—increases viscosity of blood
   1. anemia,
   2. vomiting,
   3. acute fevers,
   4. small fluid intake;

(d) failing heart;

(e) hypothyroidism.

In both phlegmasia alba dolens and thrombosis in varicose veins there is seen evidence of an endophlebitis. This is in contrast to thrombosis in deep veins of the leg where usually no infection exists, perhaps not even inflammation of the venous walls, merely an inexplicable thrombus. Ochsner has called this last phlebothrombosis and surmises that it is responsible for many unexplained pulmonary emboli.

Phlebitis migrans show a non-suppurative inflammation of a superficial vein which may not become thrombosed at all. The vein wall stiffens, becomes pipelike, and usually thrombosed. It is commonly associated with Buerger's disease, but may appear spontaneously in an otherwise healthy adult. After a variable time the thrombus canalizes and the vein wall softens to normal consistency. Soon after a superficial vein in another area may repeat the process. The aetiology of phlebitis migrans is unknown. A non-migrating thrombosis of superficial veins is also seen.

An unusual type of thrombophlebitis arises in the axillary vein when this vessel is indirectly affected by severe exertion of the upper arm. Sudden stretching of the costocoracoid liagment may indent the subclavian or axillary veins at a crucial point, cause trauma to the vessel wall or a valve, and in some manner initiate thrombosis—thrombophlebitis by effort.

The effect of the thrombosis on the vein in any case is deleterious for it destroys the valves and narrows the lumen, producing a tendency to venous insufficiency and varicosities.

Relation of symptoms to lesions.—Oedema is very noticeable in phlegmasia alba dolens and less so and more localized in deep calf

thrombophlebitis. At first sight this finding would appear easily explained by the occlusion of the main or very important vein of a limb, and the consequent rise in venous hydrostatic pressure with damming back of the tissue fluids. Ochsner has shown that this may be contributory, but certainly not the main factor. Experimentally he has occluded the principle vein of the limb without securing any oedema. On the other hand, he offers a very pretty explanation for oedema, pain, and pallor of the affected limb. The venous thrombus stimulates afferent nerves innervating the vein's wall reflexly through the sympathetics, set up vaso constrictor impulses that cause spasm of the associated arteries. Consequently, the limb and its vessels suffer from anoxia due to the persistent arterial spasm.

This increases the permeability of the capillary walls and allows transudation of plasma proteins and electrolytes. Venous spasm accompanies the thrombosis, both increasing the intravenous hydrostatic pressure to four or five times the normal and so contributing to fluid retention in the tissue spaces. Cessation of arterial pulsations, as we have here, results in diminution of fluid movement in lymph vessels and lymphatic stasis. The limb is now at its lowest drainage efficiency. In support of the Ochsner hypothesis are the excellent results in treating the spasm with injection of procaine into the sympathetic ganglia supplying the limb. Symptoms of thrombophlebitis of the femoral vein abate in startlingly short order with the procaine injection breaking the spasm. That arterial spasm does exist has been observed experimentally and found clinically in several cases by Leriche. In one of the latter's patients thrombophlebitis of the femoral vein was associated with gangrene of the limb. On dissection there was found venous thrombosis but no organic arterial occlusion. It was supposed quite soundly that the gangrene was due to the arterial spasm.

The pain and pallor of the limb (especially of milk leg) are supposedly due to ischaemia brought on by the arterial spasm. Pain may also be directly caused by the thrombus irritating afferent nerves of the venous walls.

Summary of Ochsner's Cycle

Venous thrombosis:

1. venous spasm,
   (a) increased venous pressure oedema;
2. reflex arterial spasm,
   (a) anoxia with increased capillary permeability—oedema,
   (b) anoxia—ischaemia with pain and pallor,
   (c) cessation of arterial pulsations with lymphatic stasis—oedema.

This cycle is continuous until the spasm is broken by anaesthesia of the sympathetic nerves.

Homans has observed in many cases of phlegmasia alba dolens and deep calf thrombophlebitis the presence of a perivenous inflammatory exudate. This inflammation would naturally increase the capillary transudation and thus the oedemia. However, the usual circumstances is not to find a perivenous inflammation and in the majority of instances Ochsner's theory of vasospasm stands up securely.

When fever is present it is associated with an endophlebitis as in milk leg. Deep calf vein thrombophlebitis is characteristically free from infection and temperature rises. The fever is considered a manifestation of an infection, not a thrombosis.

Sequelae

The most frequent course under a modicum of treatment is canalization of the thrombus or a sufficiently increased collateral drainage to assure recovery. Not all end so happily, the common complications being: (1) pulmonary embolism, (2) post phlebitic oedema, (3) post phlebitic induration and ulcer, (4) infection of the thrombus.

Pulmonary embolism.—Pulmonary embolism is a most dramatic but comparatively infrequent sequel of deep thrombophlebitis. The body of the embolus is derived from the soft propagating part of the thrombus. This detaches in part or "in toto" and is carried along by the slowly circulating stream to the fast flow of the large veins. Eventually it reaches the pulmonary arteries which it may occlude, or pass through to the lung forming a large infarct. The pulmonary arteries are of large calibre and only clots arising in the inferior vena cava or common iliac veins could occlude them. Aschoff keenly makes the point that the plugs in the pulmonary arteries are *folded thrombi.* Unraveling one of these we see the clot that became an embolus is 2 cm. in diameter and 35 to 40 cm. in length. These proportions correspond to the size of a long medium-sized vessel like the femoral vein. By rolling up into a segment several times broader than the original thrombus, the embolus can successfully block the pulmonary arteries. Sometimes the physician is forewarned of the disaster of embolus by symptoms of multiple lung infarctions occurring on preceding days. The life-saving procedure recommended is ligature of the external iliac vein.

The embolus usually arises from the clot in the deep calf veins and, less commonly, from the femoral-iliac thrombus of milk leg. Very rarely if at all does an embolus start from the long saphenous vein and varicose vein thrombi, and only occasionally from a migrans type. The sclerosis of the varicose vein wall, the inflammatory adhesion of thrombus to wall, and the back pressure *on the thrombus,* in an incompetent varicose venous system all militate against embolism.

Allen states that once thrombophlebitis is clinically manifested pulmonary embolism is not the order of the day. This may very well be true as far as phlegmasia alba dolens is concerned, for here symptoms are closely related to the endophlebitis. Once the inflammation is noted mural adhesions have already bound the thrombus which itself is hardened and more coherent. Deep calf vein thrombophlebitis may, Homans says, be symptomatic and at any movement furnish a pulmonary embolus. Murray and Best are in complete disagreement with Allen.

Post phlebitic oedema.—If Ochsner's cycle of vasospasm-oedema is unbroken there is great possibility of long persisting oedema. Should this occur the protenized oedema fluid will itself excite a non-infectious inflammation. The presence of this fibrous tissue is in itself a mechanical barrier to adequate drainage and cause perivascular and perilymphatic fibrosis. The fibrosis probably constricts the thin-walled capillaries of the venous and lymphatic systems and so preserves the oedema. The involved limb becomes woody and remains larger than its mate.

Post phlebitic Induration and Ulcer.—After a deep thrombophlebitis a good number of superficial veins enlarge and act as new routes of venous return. Should the strain on the communicating veins, connecting the deep veins to the superficial ones, be too great they, as well as the superficial veins dilate, become tortuous and insufficient. The area is subsequently poorly drained and the venous stasis present may be an important factor in the formation of an indurated area of skin. Induration leads to ulceration. Both may occur in three months to twenty years after the phlebitis. They are found to arise either in an area of residual swelling or spontaneously along the inner third of the lower leg. The indurated skin becomes pigmented brown and thickened. The subcutaneous tissues are hardened, fading into the normal surroundings, or are well defined by raised scalloped borders. Soon with slight trauma to the skin a shallow ulcer is formed. It is at first easily healed by elevation of the leg. Recurrent ulcerations follow until the area presents a chronic ulcer a few centimeters in diameter or completely encircling the leg. The base is covered with a dirty gray exudate and is secondarily infected. The surrounding skin is indurated, cyanotic and pigmented. The ulceration is preserved by venous stasis and possibly a superimposed fungus infection. The treatment is surgical. Ligation of the long saphenous vein and the varicose communicating veins of the lower leg is curative. Fungicides must be used to maintain the integrity of the healing skin.

Infection of a thrombus.—This is very unusual and of grave significance. Suppurative disintegration of a thrombus leads to pyemia and septicemia. The treatment is ligation of the vein proximal to the infected thrombus and its excision.

Treatment

1. *Femoro-Iliac Thrombophlebitis.*—Phlegmasia Alba Dolens has long been a subject of therapeutic experimentation and the literature reveals a startling multiplicity of methods, each of which has given good results—in the hands of its proponent. Ochsner and DeBakey have reviewed and evaluated the various methods, and devices that have been tried. It is not our purpose here to detail all of them, but simply to outline those which seem to have survived beyond their original publication and to have a rational basis.

(a) Prophylaxis

As applied to thrombophlebitis, this means simply the avoidance of those factors which either favour or precipitate thrombosis in a vein. Its importance is self evident.

To recapitulate briefly: the factors involved in thrombosis are changes in the blood plasma, the blood elements, the blood flow, or in the vessel wall itself. Certain of these changes are unavoidable, the exciting cause: childbirth, operation, injury or debility, the anatomic and physiologic peculiarities in the venous return from the legs, and the enforced stay in bed. Others are more or less preventable, and it is against these that our efforts must be especially directed.

1. GENERAL PROPHYLACTIC MEASURES:

(a) *The maintenance of blood volume.*—Dehydration occurs postoperatively much more frequently than is generally supposed, although it is usually not severe enough to provoke attention. Even a slight dehydration increases the viscosity of the blood, and so it is very important to maintain an adequate fluid intake either orally, by rectum, by interstitial, or by intravenous, hypodermoclysis.

(b) *The prevention of excessive venous stasis.*—Immobilization with its consequent muscular inactivity is a second, less amenable postoperative condition. Also, the maintenance of a posture such as Fowler's position adds to the circulatory retardation. Therefore, early movement of the legs, and perhaps even exercise in bed, coupled with elevation of the legs at least part of the time, is advocated.

(c) *The prevention of excessive intra-abdominal tension.*—This must start right at operation—with perfect wound closure. Loose dressings are then to be preferred to tight, constricting bandages and, if abdominal wounds are carefully closed, tight strapping is unnecessary (Bancroft). Another danger is the common occurrence of postoperative intestinal distention due to loss of intestinal tone. This may be forestalled by careful handling of the abdominal viscera at the operating table, and the early use of solid food. Prompt treatment of ileus by an indwelling rectal catheter and pituitrin will minimize its ill-effects.

(d) *Maintenance of respiratory activity.*—Diminished respiratory activity is a serious factor in retarding the blood flow. The simplest way to overcome this is by instructing the patient to take deep breaths at frequent intervals. Carbon dioxide inhalations for a few minutes every hour are also recommended as a stimulant to respiration.

(e) *The application of heat.*—Ochsner routinely uses heat applications in the form of a heat tent over the abdomen and lower extremities. The value of the heat is said to lie in increasing the tone of the intestine, and in producing vasodilatation of the peripheral vessels which speeds the blood flow through them.

2. SPECIFIC MEASURES:

(a) *Sodium Thiosulphate.*—More specific, withal more expensive, measures have been based on anti-coagulant activity. In 1935 Bancroft reported a method of determining the clotting tendencies of the blood by estimation of the plasma clotting index and fibrinogen content of the serum. When these are found to be high there is believed to exist an increased tendency to thrombosis and special precautions, or an anti-coagulant drug are indicated. A high protein, low fat and carbohydrate diet may be instituted and ten cc. of a ten per cent solution of sodium thiosulphate is administered intravenously on three successive days, the series being repeated after an interval of one day if the bleeding factors remain high.

(b) *Hirudinization (the use of leeches).*—The Hirudin secreted by the salivary glands of leeches is known to be an anti-coagulant in *vitro*. Whether it retains that effect for very long in the body is a matter of speculation. Many authors consider it to be a valuable prophylactic.

(c) *Heparin.*—Heparin is at present obtained from ox lung. This substance, when administered intravenously, not only delays coagulation time, but also prevents adhesion of the thrombocyte, thus completely abolishing thrombosis. By its use Murray and Best have found that the incidence of thrombosis is decidedly reduced. In 400 cases no thrombosis or embolism occurred if the patients were free from it at the beginning of treatment, and in the others there was no extension of the process. However, the rapidity with which heparin is destroyed in the circulating blood makes it necescsary that it be administered by continuous intravenous drip. A high concentration must be maintained, and the treatment must be instituted very soon after operation. Heparin will not dissolve a blood clot or thrombus and it is assumed that if all bleeding has been stopped at the time of operation heparin will not start a haemorrhage. There still remains the possibility that vessels which do not bleed while the circulation is depressed at operation may do so with a rise in blood pressure. For these reasons heparin is not administered for from four to 24 hours following operation. The injection is

discontinued when the patient has regained normal activity. The comparatively small series so far reported allows no definite conclusions to be drawn, and the great expense (about $80 per patient) make this form of treatment impractical for general use.

To sum up the prophylaxis of thrombophlebitis: we have two groups of preventative measures, the one, simple and inexpensive, the other complex and expensive. Keeping in mind that 19 out of 20 cases wherein one or more of the aetiological factors is present will not develop the disease, but that we must continually watch out for the 20th case, it is suggested that the simple, inexpensive measures be made routine. In this regard it should be emphasized that measures against thrombosis, to be effective, must be instituted at the earliest possible moment, not several days after the exciting factor has appeared. The Bancroft procedure may be applied to select those cases which are most likely to develop thrombosis and in these heparin, herudin or sodium thiosulfate may be used as indicated.

(b) The treatment of established thrombosis

Our therapeutic aims now are: (a) To minimize the discomfort of the patient, (b) To prevent embolus, (c) To shorten the course of the disease, (d) To prevent undesirable sequelae.

1. *Elevation of extremity.*—This is the most important single item in the treatment for two reasons. First, it minimizes the danger of an embolus breaking off by hurrying the blood stream past the proximal end of the thrombus and thus preventing the jutting forth of a fragile clot. Secondly, it relieves oedema by favouring lymphatic drainage.

2. *The application of heat.*—Heat is preferable to the old-fashioned application of ice bags. Heat brings more comfort; it hastens the blood flow, and the normal involution process of both the thrombus and the phlebitis. It may be applied continuously from foot to groin.

3. *Immobilization.*—This is very difficult to achieve, and is probably not as essential as was formerly believed. Its rationale was to prevent any movements which might lead to the breaking off of an embolus. However, as Homans points out, the proximal end of the thrombus being within the pelvis, it is little influenced by movements of the leg. Furthermore. the necessary movements, which the patient must daily perform anyway are far greater than any slight casual exercise which might be prevented by rigid immobilization.

4. *The use of leeches.*—This form of therapy has been widely used in Europe and in many clinics in America with varying degrees of success. Hirudin, besides being an anticoagulant, is said to also have the property of dissolving blood clots. Other observers ascribe the good results to the local blood letting, or to the prevention of venous spasm.

Still open to debate is the contention of some authorities that leeches applied to a leg in which thrombophlebitis is present are liable to excite the breaking off of an embolus.

5. *Heparin.*—Murray and Best have also used this substance in patients suffering from thrombophlebitis. It is interesting to note that it was only by chance that this application of heparin was discovered: "When looking for cases in which to test the toxicity of heparin during early stages of this clinical investigation it was considered that several cases of thrombophlebitis which were on the wards at the hospital might benefit by an intravenous saline injection and, incidentally, we might gain some information on heparin. We were greatly surprised to find that there was a marked change in the clinical course of these cases." Heparin has no effect on a thrombus once it is formed, and so the mechanism of action here is uncertain. It may be that with heparin limiting progressive thrombosis, the inflammatory reaction in the thrombus already present may burn itself out fairly quickly and the symptoms subside. Fifty cases were treated with heparin, and all received some beneficial effect. Besides phlegmasia alba dolens, this series included cases of phlebitis migrans, deep thrombophlebitis and thrombosis in varicose veins. In all groups the acute symptoms subsided very rapidly and there was no pulmonary embolism and less residual oedema than usually occurs. There was no recurrence except in the migrating type.

A ten-day course of heparin is advocated, and, as mentioned above, the prohibitive cost of the substance markedly limits the application.

6. *Acetyl-Beta-Methyl Choline Hydrochloride (Mecholyl).*—This vaso-dilator, applied by iontophoresis, has been advocated by Murphy and others who report excellent results. It probably has greater application in the treatment of post-phlebitic induration.

7. *Artificially induced fevers.*—Sterile milk and typhoid vaccine injections have been used to procure vasodilatation. This seems to be a rather roundabout and dangerous method of approach in view of the fact that the problem is purely a local one.

8. *Mechanical devices to improve the circulation.*—Paine and Levitt reported the use of intermittent venous occlusion, others the oscilating bed. While the results were good, the series of cases in which they were applied were too small to permit any conclusions to be drawn as to the efficacy of such an approach to the problem.

9. *Procaine hydrochloride block of the regional sympathetic ganglia.*—This method of securing vasodilatation was first suggested by Leriche, and the technique was worked out by Ochsner and DeBakey. Their results are remarkable in the rapidity of abatement of all symp-

toms and in the complete freedom from complications. There was no other therapy used, yet 60 per cent of their patients were completely cured in eight days, the remainder in twelve days.

In this regard we might mention the criticisms of Edgar V. Allen, who denies their concept of the predominating role played by vasospasm in the production of symptoms, and does not believe that relief of arterial spasm can hurry the convalescence. Furthermore, he states that if it should be desired to relieve arterial spasm, then anaesthetization of the lumbar sympathetic nerves is a most unsatisfactory method of doing so. Application of hot packs to the involved limb he believes to be just as efficacious, simpler and without danger.

10. *Ligation of the vein proximal to the involved process.*—This procedure should be reserved for suppurative cases which are extending or producing recurrent septic embolic due to liquefaction and breaking off of the infected clot.

The treatment of established thrombosis, then, is subject to much dispute and experimentation. For the present the time-honoured heat and elevation may be recommended as logical cornerstones on which to lay the basis of therapy. We might add sympathetic block, mecholyl iontophoresis, heparin or leeches as measures whose value is not yet fully assessed, but whose rational basis in pathology and pharmacology suggest their usefulness.

(c) The after-care of Thrombophlebitis

The primary objective now is to prevent chronic venous insufficiency of the limb which manifests itself in such disagreeable fashion. Barker and Counseller believe that the patient should not be kept in bed longer than ten to 18 days. Longer periods favour the production of further episodes of thrombosis and embolism, the development of muscle atrophy, osteoporosis and post-phlebitic neurosis.

A good plan is to encourage active exercise of the leg in bed, as the oedema disappears. This should be continued, with assistance if necessary, for some days before the patient gets up. The patient is allowed up when the temperature has been normal for four days, all swelling has disappeared from the leg below the knee, and there is no pain or tenderness over Scarpa's triangle, or in the region of the great veins distal to it. Two types of support are recommended. More practical is the heavy, pure rubber bandage applied over a cotton stocking from the toes to the knee, with only a small portion of the heel exposed, and the shoe overlapping the lower margins of the bandage. The other type is the heavy elastic bandage which is more comfortable than rubber, especially in hot weather. However, this bandage is expensive, loses its elasticity in a few months, and is practically useless if not applied correctly.

The support is worn whenever the patient is up and around. Full use of the legs must be only slowly and gradually attained. One day each month the patient may try going about without the bandage, and whenever oedema does not recur may discontinue its use entirely.

THROMBOPHLEBITIS IN THE DEEP VEINS OF THE LOWER LEG

(a) *Conservative treatment.*—These measures are to be applied to all cases in which the patient is seen during his first attack. Complete bed rest, with the feet elevated until all soreness and oedema is gone, is followed by several days of gentle exercise of the leg in bed. The patient is now allowed up wearing an elastic bandage. He alternates periods of walking with periods of rest and elevation, gradually decreasing the latter until active life is resumed.

(b) *Radical treatment.*—If the above regime fails, *i.e.*, the oedema and blueness return; or if the patient is seen late and has for several weeks been undergoing successive cycles of apparent recovery during elevation, and return of the original signs afterwards, then divide the femoral vein distal to the profunda. This procedure hastens cure and removes the danger of embolism. After healing of the wound, an elastic bandage is worn for a few weeks only.

THROMBOPHLEBITIS IN VARICOSE VEINS

(a) *Palliative treatment.*—Bed-rest with elevation of the feet and the application of heat is best. In selected cases with the process confined to the lower leg, an elastic bandage may be applied, and the patient allowed a guarded active life.

(b) *Curative treatment.*—This consists in ligation and resection of the saphenous vein at the femoral junction, just as is done in an uncomplicated varix. It must not be used in cases with thrombosis extending high in the thigh until palliative treatment has brought about a disappearance of all local thickening and tenderness.

Superficial Thrombophlebitis and Phlebitis Migrans.—The treatment of the latter condition is usually very unsatisfactory, the process seeming to go on no matter what measures are tried. Elevation of the lower extremity for two weeks may be of value. In cases already present for several weeks it is best to ligate and divide the saphenous vein.

Axillary Thrombosis.—In the acute stage the treatment, as in the lower extremity, consists of rest, heat and elevation. Block of the sympathetic ganglia with procaine hydrochloride is also applicable in this condition. If there is residual oedema an elastic bandage or diathermy may be used.

Summary

We have as briefly as possible summarized the more common thrombophlebitides. Current concepts of pathogenesis and treatment have been stressed.

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Acute Peripheral Arterial Occlusion and Its Treatment*

By KENNETH D. SYMINGTON, B.A., '40

AN attempt is made in this paper to discuss various aspects of acute, embolic, major arterial occlusion in the extremities, an emergency in every sense of the word, which, although not a frequent occurrence, demands early diagnosis, immediate and adequate treatment if the patient's limb is to be spared. Murray[4] places embolism of the sacral arteries next in importance only to external and internal haemorrhage as one of the most urgent surgical emergencies. The series of events following embolism end in peripheral tissue ischaemia, to which is attributable the seriousness of embolism. Ischaemic tissues die within a few hours of the complete removal of their blood supply. In contrast, common abdominal emergencies such as ruptured viscus, acute appendicitis or intestinal obstruction, while better treated at the first possible moment, will produce equally disastrous results only after a lapse of six or eight hours.

Of 126 recorded cases of embolism at the Toronto General Hospital over a five-year period the emboli were found in the pulmonary vessels in 56 cases, cerebral in 35, peripheral arteries in 30, central artery of retina in three, and coronary arteries in two.

AETIOLOGY

An embolus was defined by Welch as the impaction in some part of the vascular system of any undissolved material brought there by the blood current. A thrombus originating in the veins, the heart, or the arteries is the origin of the great majority of emboli. Detached atheromatous plaques, clumps of tumour cells or bacteria, fat globules, parasites and air bubbles occasionally, however, play the part of an embolus.

In the present discussion we are limited by the nature of the subject to the consideration of emboli of sufficient size to produce major arterial occlusion. The only type of embolus large enough is a dislodged thrombus or fragment thereof, and such an embolus is nearly always the result of cardiac or arterial disease leading to thrombus formation within the left heart or arterial tree. Atheromatous plaques rarely are detached from their site of origin in the aortic wall to lodge in a large peripheral artery. Air-bubbles, fat-globules, clumps of tumour cells or bacteria acting as emboli are of negligible importance here. Paradoxical embolism, originating on the venous side of the systemic circulation

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but attaining the arterial side through a patent foramen ovale (a congenital septal defect not incompatible with life), is a pathological oddity, though capable of being an aetiological factor.

A recent study of 30 cases of peripheral embolism by Murray[4] revealed that heart disease was responsible for the embolus formation in 83 per cent, and his figures agree very closely with those of other observers. The cardiac lesions giving rise to peripheral emboli are, in the order of their importance, auricular fibrillation, mitral stenosis, rheumatic myocarditis, coronary thrombosis, and subacute bacterial endocarditis. Of these lesions, auricular fibrillation is the cardinal factor. Another event which often gives rise to embolism is mural thrombosis occurring on the endocardium covering the base of a myocardial infarct following coronary occlusion. Embolism follows auricular thrombosis when a sudden change in the rate of flow of the blood in the fibrillating heart accompanies the onset of normal cardiac rhythm. Such a change may be spontaneous, or the result of digitalis or quinidine therapy. The force of the normal auricular contraction wave serves to force the thrombus through the mitral valve into the systemic circulation. Mural thrombi are easily dislodged by similarly augmented cardiac contractions.

Thrombi originating in the arterial tree proper form as a result of primary mechanical, chemical or bacterial trauma to the vessel's endothelium, in a manner exactly analagous to their intracardiac formation. Dislodgment of thrombi from ulcerative lesions of arteriosclerosis, from syphilitic vessels, from an aneurysm or from arteriosclerotic, injured or infected vessels, result in emboli actually originating within the arterial tree.

The three main factors in any thrombus formation are:

1. *Primary damage to the intima of a blood vessel.*—This furnishes the essential nidus for thrombus formation. Bacterial destruction is the preponderantly common factor, and herein lies a strong connecting link between peripheral arterial embolism and organic disease of the left heart. The organism causing the rheumatic lesions in the heart produces the necessary injury to the chamber wall and so paves the way for thrombosis. Similarly a bacterial aortitis or arteritis of the great arteries of the trunk may involve the endothelium and damage it.

2. *Change in rate of blood flow.*—Mere slowing of the blood will not of itself produce true thrombosis, but it acts as a very potent predisposing factor. Slowing of, or obstruction to the blood flow, especially when it results in the formation of eddies, allows the platelets to settle out and agglutinate. One may realize from this why auricular fibrillation is so important a factor in peripheral embolism—the platelets tend to become precipitated and agglutinated by the greatly decreased

(almost static) blood flow in the fibrillating auricles, or by eddies produced by leaking or deformed valves. Many observers believe that a combination of this factor and endothelial damage must be present before a thrombus will form.

3. *Changes in physical and chemical properties of the blood.*— Increase or decrease in blood viscosity, alteration in quantity or quality of the platelets, infection, metabolic disease, some debilitating disease or peripheral arterial disease itself are all factors here. It is not likely that any of these factors has much to do with intracardiac thrombosis. Their main effect is to alter the platelets quantitatively and qualitatively so as to favour agglutination, and anything favouring agglutination will be a large factor in thrombus formation.

PATHOLOGY

As large arteries branch there is a rapid decrease in the calibre of the distal segment. It is at such segmental constrictions and at the bifurcations of the arterial tree that emboli tend to lodge, the commonest locations of all being at the bifurcations of the aorta and common iliac arteries. Passage of the embolus into the large branches of the aortic arch is rather uncommon. Because the external iliac artery is the direct extension of the common iliac, emboli pass along it to wedge at its bifurcation into the femoral and profundus branches, or more distally at the bifurcation of the popliteal artery. In the arm lodgment tends to occur at the origin of the superior profunda brachii or the bifurcation of the brachial artery in the antecubital fossa.

The embolus produces an irritation which results in sudden, violent constrictor spasm of the vessel distal to the point of lodgment. This angiospasm is probably the origin of the initial severe pains, and it may lead to complete occlusion of the lumen. If the lumen still remains partially patent so that some blood passes the initial obstruction to deposit platelets distally, a secondary thrombosis is produced which completes the occlusion and may extend the mischief by obstructing distal collateral branches. Similarly the secondary thrombus may build up proximally to further embarrass anastomotic circulation.

The conclusions drawn by one group of workers (Cornil *et al*[6]) studying the histiophysiology of parietal arterial wall reactions subsequent to complete embolic occlusion are pertinent:

> "In the case of the aseptic embolus, the process was dominated by hystiocytic infiltration and capillary changes in the adventitia, and by degenerative changes in the media. These lesions are dependent, then, on the suppression of the endovascular blood current, which results in adventitial and mesarterial trophic changes. The reactions following a septic embolus were distinguished by a polynuclear infiltration of the embolus itself, by an early endothelial inflammatory change, degeneration of the media, and a polynuclear infiltration of the adventitia and media. The result was a poly-

> nuclear infiltration within the lumen of the vessel, within its walls, and on the outside of the vessel, with the combination of both trophic or mechanical and infectious factors in the production of the lesion."

These adventitial changes were found to be at their height at the end of six days in the aseptic lesions, but at the end of twelve hours in the septic lesions. These experiments enabled the writers to arrive at precise, important conclusions as regards the relative therapeutic value of embolectomy, arteriectomy or sympathectomy, as we shall see later when treatment is discussed.

The usual consequence of untreated arterial occlusion is infarction of the organ or gangrene of the extremity, depending upon the size of the occluded vessel, its situation, the number of plugged branches, the cardiac efficiency, and the number of available, dilatable collaterals —if the vessel is not an end artery with no possible anastomotic branches.

SIGNS AND SYMPTOMS

1. *Pain.*—A major arterial embolic occlusion was described by Buerger in 1911 as being associated with sudden pain, blanching, and coldness of the limb, and most subsequent writers have described a similar syndrome. McKechnie[3] points out, however, that:

> " . . . a broader view must be taken when entering into a discussion of the symptoms of acute arterial obstruction, as the symptoms frequently are not acute and the condition is not always accompanied by pain."

Linton[1] found 67 per cent of patients in his series to have had an initial excruciating pain in the affected limb, and Murray[4] reports such pain in 33 of his 37 cases. These data reveal that embolism cannot be ruled out because of the absence of sudden excruciating pain.

Such pain is, however, the common initial symptom of the accident. It varies from an indefinitely localized ache, due probably to an incomplete occlusion, to an agonizing pain suddenly felt at a definite location and radiating peripherally along the course of the acral vessels. This latter pain accompanies a sudden complete blockage of a main artery and the immediate angiospasm. A sudden local pain extending down the limb is probably the result of a partial occlusion with ensuing arteriospasm progressing to the periphery, leaving the vessels in the contracted state found at operation. Anoxemia of tissues produces the widespread aching and increasing dull pain experienced in spite of sedation until relieved by restoration of the circulation or onsetting gangrene.

2. *Paraesthesiae.*—Sudden changes in sensation such as numbness, tingling, coldness or stiffness of the extremity are reported by Murray[4] as the initial symptoms in four of his 37 cases. These he thought due to a very small saddle embolus which only slightly impaired the circula-

tion initially. Symptoms of anoxemia developed within four hours as a result, probably, of secondary thrombus formation completing the occlusion. Embolic obstruction at the bifurcation of aorta or common iliacs onsetting with paraesthesia only is accounted for by the relative lack of muscle tissue and the preponderance of fibro-elastic tissue in the media of such large vessels preventing a painful arteriospasm as occurs in the smaller, more muscular peripheral vessels. It is apparent, therefore, that initial numbness and tingling followed by increasing widespread dull pain are far graver prognostic symptoms than is excruciating pain.

3. *Skin colour changes.*—The changes usually seen in the skin in the presence of a sudden complete occlusion are pallor of the distal parts, a cyanotic band farther up, and proximally an area of blotchy mottling fading into normal colour. The upper margin of colour change is of great significance in helping to decide the level of the obstruction if one remembers that the normal skin colour extends considerably more distal on the extremity than the level of the block, due to the collateral circulation. In the absence of any colour changes in the skin it may safely be assumed that there is no lesion endangering the tissues of the limb.

4. *Temperature changes.*—These changes, measured by a mercury thermometer or thermocouple, are also valuable aids in localizing the level of the block. The distal pallid area rapidly cools to room temperature. Over the more proximal areas of cyanosis and blotchy mottling the temperature only attains normal at the level of normal skin colour.

5. *Loss of pulsations.*—Pulsations in peripheral arteries used in conjunction with skin colour and temperature changes are probably the most valuable localizing sign, and usually suffices to localize the lesion. If, as in an obese patient, careful palpation to detect where the pulsations cease is not satisfactory, the ordinary sphygmomannometer or the oscillometer will be found to be valuable aids.

Less reliable and inconstant signs and symptoms are the sensory changes, paralyses, constitutional changes, and the absent skin and tendon reflexes. Though used by several investigators, arteriography is not advised. The radium content of the thorium dioxide in these radiopaque substances has prevented their acceptance by the U. S. Pharmacopeia.

Few, if any, signs of shock are found unless the unusually severe type of pain is experienced. The patient's facial colour is good, and unless cardiac decompensation has set in, the pulse rate is not alarmingly elevated. The oral temperature remains within normal limits, and the patient is usually wide awake, alert and apprehensive. The

general appearance of the limb is aptly described as lifeless. Its veins are collapsed and it is held immobile.

DIAGNOSIS

Ordinarily a careful study of possible aetiological factors, the history of onset, the subjective and objective findings will lead to a correct diagnosis. In this regard McKechnie[3] makes some important observations:

> "In order to make the diagnosis early it is not necessary for the physician to have an accurate and widespread knowledge of the symptoms and pathology of sudden arterial occlusion. Rather, all that is necessary is the knowledge that the symptoms are sufficiently varied, so that if some unusual occurrence directs his attention to the limb he will carry out a thorough examination, particularly of the acral arteries, and will rely on the examination rather than the history for the diagnosis of occlusion. . . . Absence of pulsations below a given point in an artery is indicative of arterial occlusion, if a normal arterial tree always is assumed to begin with. If this absence of pulsation is associated with abnormal pallor and decreased surface temperature, then the diagnosis of recent arterial occlusion is justified. Other findings are confirmatory but not individually diagnostic."

Differential diagnosis should exclude anomalies of the arterial tree, previous peripheral vascular disease with thrombosis or thrombophlebitis, arteriosclerotic gangrene, Buerger's disease and Raynaud's disease.

TREATMENT

(a) MEDICAL.—Generally, the medical therapy of major arterial occlusion is aimed at the relief of pain, the prevention of infection of ischaemic tissues, and the re-establishment of an adequate collateral arterial circulation.

1. *Relief of pain.*—Angiospasm seems to result from activity of the sympathetic nerves, and procedures that will paralyze these nerves are indicated. They include administration of vasodilators such as papaverine hydrochloride (eupaverine) in ½-grain doses intravenously, the anaesthetic infiltration of the regional sympathetic chain, spinal anaesthesia, and deep general anaesthesia.

2. *Prevention of infection.*—The limb itself should be treated aseptically and with the utmost care. It should be wrapped in cotton and placed under a heat cradle with the temperature not in excess of 105° F., for the devitalized and anaesthetic tissues are very prone to injury by physical trauma.

3. *Re-establishment of an adequate arterial bed.*—The use of passive vascular exercise as provided by the *Pavaex* machine has been highly successful. The limb, sealed inside a glass boot, is subjected to intermittent positive pressure of 20 mms. of mercury alternating with negative pressure of 80 mms. To facilitate venous return and

dilatation of the collateral vessels by local hyperthermia, the leg and boot are raised one foot above heart level, and air pre-heated to 104° F. is introduced. Not only does *Pavaex* increase the size and number of useful collaterals, but it offers the great advantage of overcoming temporary vasospasm, almost immediately ending the agonizing pain without shock to the patient. The severity of ischaemia and urgency for circulatory restoration determines the length of treatment, which, in most cases treated exclusively by this method, is continuous for 70 - 100 hours with rests of but one to two hours daily. Acute or sub-acute thrombophlebitis, Buerger's disease or arteriosclerosis absolutely contra-indicate *Pavaex* therapy, and it is of little value in angiospasm of central origin or of inflammatory disease of the vessels.

Concerning the value of medical treatment, most writers agree that the measures outlined above may always be tried out pre-operatively, but if within one hour no results are obtained, surgical intervention becomes imperative. Positive indications for perseverance with medical therapeusis are also the contra-indications to embolectomy. They are: multiple embolism, uncertainty of diagnosis, too great a lapse of time between occurrence of embolism and operation, or associated myocardial decompensation and similar organic conditions contra-indicating surgery of any kind.

In cases which show a high incidence of embolism statistically, good results have been obtained by Bancroft and others[11, 12, 13] by the use of a prophylactic medical regimen, including intravenous sodium thiosulfate, fluids in large amounts ad lib, and a low fat and carbo-hydrate diet. Heparin is probably less practicable in this group of cases than is the sodium thiosulfate.

(b) SURGICAL.—The rationale of embolectomy is based on the premise that early, safe and satisfactory restoration of main arterial channels will produce the best possible results when compared to the establishment of collateral channels only by the *Pavaex* method. As recently as 1932 Neuhof of New York discouraged surgical treatment on the ground that most cases would be just as well without operation, but all contemporary references describe embolectomy or arteriotomy as the method of choice. Murray[4] enthusiastically states:

> " . . . Analysis of our cases supports the opinion of other writers that there are few operations in surgery so eminently satisfactory in selected cases or attended by such potentiality for good as embolectomy for arterial embolus."

To be successful the operation must be performed at the earliest possible moment after the accident, for the passing hours each add to the difficulty of removal occasioned by the endothelial and mesarterial lesions accompanying the so-called "embolic arteritis," as we saw above. These rapidly progressive endothelial lesions also increase the danger

of post-operative secondary thrombosis. It seems, from recorded cases, that a lapse of more than six hours makes the outlook very unfavourable. That the underlying heart condition giving rise to embolus formation is one that offers the constant threat of formation of new emboli to again obstruct an artery upon which embolectomy has been performed, is a consideration not to be dismissed when this operation is contemplated. Of 282 embolectomies reported in the literature up to 1937, 85, or 30 per cent, produced favourable results.[1]

The operative technique of embolectomy is fully and well described by several writers and will not be repeated here.

The development of secondary thrombi at the site of the suture line 12-48 hours post-operatively is the most frequent reason for the high percentage of failures of embolectomy. The vicious physiopathological cycle is thereby reinitiated, and it is in the prevention of this complication that the hope for increasing successful results in embolectomy lies. French literature of a century ago records the use of "leeching" in the treatment of thrombophlebitis, and this therapy is still used. The leech injects, from its salivary glands, a proteose hirudin, which can neutralize the action of fully formed thrombin. Many leeches must be used, and though apparently successful in isolated cases, this treatment has not become reliable or practical in application.

Practical and highly promising is the research by the Toronto group of investigators into the use of the anti-coagulant heparin in thrombosis. Best and Murray have done painstakingly detailed work on this substance, and so far have obtained a uniformly potent, highly purified crystalline barium salt of heparin which demonstrated no toxicity in the human subject. Their experimental and clinical results in the use of heparin in thrombosis to date fully warrant its use and further investigation. In 1938 they reported[9] that peripheral embolism

> " . . . is a field where, from experimental evidence as well as from the results in a few clinical cases, it would appear probable that heparin can be of great assistance. Also, it might be worth while giving heparin in cases of embolism which are seen too late to have the embolus removed, in the hope that heparin will prevent extension of the thrombus and clot, and in this way assist the other measures used in restoring collateral circulation."

And in a more recent, but equally reserved, statement[10] they observed that results were such as to offer some hope of clinical usefulness. Deterrents to the more widespread application of heparin to selected clinical conditions are its prohibitive high cost—a course of treatment amounting to about 80 dollars—the discomfort of continuous intravenous, and the increased nursing care its use necessitates. The synthesis of a satisfactory artificial heparin is the hope they now hold out for overcoming the main drawback to a more widespread clinical use.

This group of Canadians has been enabled by their entirely original technique to perform successfully in a much greater percentage of cases than the best of former statistics have shown possible, not only embolectomies and arterial sutures, but arterial anastomoses and arterio-venous grafts. The future will show what a remarkable advance they have made in opening up an entirely new surgical field.

NOTE: For a detailed discussion of heparin, the interested reader is referred to J. M. Jane's article in the January 1940 issue of this Journal.

SUMMARY

1. Sudden peripheral arterial occlusion is not uncommon.

2. Although the symptoms are variable, careful observation of clinical signs and symptoms will establish a diagnosis without difficulty.

3. Early institution of adequate treatment is imperative, as neglected cases usually terminate with amputation or end fatally.

4. Embolectomy is the method of choice in early cases.

5. The anti-coagulant heparin has been experimentally and clinically proved to be a valuable adjunct to surgery in this condition, and though not yet entirely practical, promises much for the future.

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The Hypothalamus

By ALAN DOUGLAS, '42

CLAUDE BERNARD,[1] toward the close of his long and useful life of pioneering in the fields of the new physiology, said: "The fixedness of the internal medium is the condition of free life. All vital mechanisms, however varied they may be, have only one object—that of preserving constant conditions in this internal environment."

Receiving afferents from the ascending sensory tracts by way of the thalamus and subthalamus, and giving rise to efferent tracts which either directly or indirectly affect the activity of the entire autonomic nervous system, the hypothalamus integrates the individual activities of viscera, endocrines and smooth muscle with reference to the economical needs of the whole organism. Such an integration of the body's internal medium serves to maintain what Cannon[2] calls homeostasis, which has as its basis the doctrine that all external activity must necessarily be measured in internal adjustment.

Related directly to the hypophysis and indirectly to the other glands of internal secretion, the hypothalamus

(1) regulates endocrine functions and their inter-relations,

(2) regulates and integrates conservating autonomic functions,

(3) is concerned with teleologically defensive and protective reactions which we term emotions, and

(4) influences the activity of the cortex in regulation of degree of wakefulness and excitation.

Although the sensory and motor systems are concerned with the relationship of the individual to his environment, they operate under the influence of the autonomic system serving to free the internal conditions of living from tensions created by external events. Or, as Cannon[4] states, "When the activity of the exterofective system disturbs the fluid matrix of the body, it is the function of the sympathetic to maintain homeostasis by its interofective functions." This the hypothalamus supervises.

Kempf[3] has aptly summarized Cannon's views on homeostasis by saying that "any form of potentially harmful stimulus, whether it stimulates the visual, auditory, gustatory, cutaneous, or the entero- or proprioceptive fields, tends to cause an immediate fear or avertive reaction which is promptly followed by a compensatory reaction, which either removes the offending stimulus from the receptor (fight) or the receptor from the stimulus (flight). In order that this vitally necessary procedure shall be quickly and safely accomplished, the autonomic

apparatus has developed the capacity to compensate by increasing the amount of glucose and adrenalin in the blood, by increasing its coagulability, by regulating and redistributing the blood supply so that organs necessary for the immediate struggle shall be given an increased blood supply, by appropriately changing the blood pressure, by increasing the rate and amplitude of the heart beat, and by increasing the dilatation of the bronchioles and the working powers of the muscle cells.

It is our purpose to discuss briefly the hypothalamus as the central regulator of this all-important internal environment together with some of the commoner signs and syndromes of hypothalamic dysfunction.

ANATOMY

The hypothalamus comprises a relatively small area on the ventral aspect of the diencephalon—the floor and the lower parts of the lateral walls of the third ventricle. It is delimited dorsally from the thalamus proper by the hypothalamic sulcus and laterally by the internal capsule and the subthalamic region. To the naked eye, its ventral aspect presents the optic chiasm, the tuber cinereum, the infundibulum or pituitary stalk, the mamillary bodies and the posterior perforated substance to the interpeduncular fossa. Rostrally it blends with the pre-optic area and it is not yet certain where the dividing line is between these two regions.

The nuclei are divided into three groups according to their position:

(a) ANTERIOR GROUP:

1. *Preoptic nuclei.*—These lie between the lamina terminalis anteriorly and the supra-optic group posteriorly. The medial nucleus lies just beneath the ependyma of the third ventricle; the lateral are more deeply situated.

2. *Supra-optic group:* (a) Paraventricular.—This nucleus is one of the largest and oldest phylogenetically of the hypothalamic nuclei. It extends forward to the anterior commissure, upward to the sulcus terminalis and below to within two or three mm. of the optic chiasma. Scharrer stresses the frequency of multinucleate cells in this nucleus, which he says arise by amitotic division, and describes inclusions of a colloid nature suggestive of an excretory function. These may be related to Cushing's idea of a non-vascular connection between the pituitary and the hypothalamus discussed below.

(b) Supra-optic nucleus proper.—This cell mass lies in the anterior part of the floor of the third ventricle straddling the optic chiasma. It is represented by a group of large cells lying anterior to the chiasm and a group of smaller cells posterior to it.

Axons from both these nuclei pass down the infundibulum to the

pituitary stalk and thence to the pars nervosa of the gland, and also down the brain stem to the parasympathetic cranial nerve nuclei. Possibly, also, they contribute to the efferent outflow to the nucleus parasympathicus of the sacral cord.

(b) THE MIDDLE GROUP:

1. *Tuber group:* (a) The ventromedial hypothalamic nucleus lies between the supraoptic group in front and the posterior hypothalamic and mammillary nuclei behind. It is composed of small rounded or oval cells with poorly staining cytoplasm.

(b) The dorsomedial hypothalamic nucleus is cytologically the same as the above but lies just beneath the ependyma of the third ventricle. Axons from these nuclei as well as from the lateral hypothalamic area pass to the parasympathetic nuclei of the brain stem and to the nucleus parasympathicus of the sacral cord.

2. *The Lateral hypothalamic area.*—This region is composed of several nuclei which are difficult to distinguish one from the other and will not be designated separately. Among them, however, is the tuber nucleus which is quite prominent and particularly well developed in man. These nuclei of the lateral hypothalamic area lie deep to all others on a plane about the same as that of the columns of the fornix.

It is from this middle group that the majority of visceral reactions have been obtained on foradic stimulation—a few of which will be referred to below.

(c) THE POSTERIOR GROUP:

1. *The Posterior hypothalamic nucleus.*—This nucleus lies just above and just rostral to the mammillary bodies and is composed of a dense matrix of small cells among which are scattered, singly or in small groups, large cells which are oval in shape and possess eccentric nuclei and cytoplasm which looks as if it were undergoing degeneration. These cells are all motor in characteristics and send efferent fibres to the intermediolateral cell columns of the cord via the reticular formation.

2. *The nuclei of the mammillary bodies.*—(a) Medial: The medial nuclei form the bulk of the mammillary bodies in man, being about five mm. in diameter. They form a homogeneous mass of densely packed small cells surrounded by a definite capsule of white matter.

(b) Lateral: The lateral mammillary nuclei are about 1.5 mm. in diameter in man and are cytologically similar to the medial nuclei. Both receive afferents from the fornix and send their efferents to the thalamus by means of the mammillo-thalamic tract.

(c) Substantia grisea centralis: Very small cells, almost devoid

of cytoplasm, whose nervous nature is betrayed by their vesicular nuclei, are to be found scattered almost throughout the whole hypothalamic area. They form the substantia grisea centralis which is a "substratum of relatively under-developed nervous cells out of which certain groups are differentiated into more or less definite nuclei."[20]

The hypothalamus receives efferents chiefly from:

(i) the cortex, particularly the frontal areas,

(ii) the anterior nucleus of the thalamus, mediating emotional and visceral activity.

(iii) the corpus striatum, and

(iv) the sensory nuclei of the cranial and spinal nerves.

The Hypothalamus from the Standpoint of Function

That reflexes of an autonomic nature are integrated and coördinated at some level between the inferior colliculi and the basal ganglia has been obvious for many years—ever since it became known that decorticate dogs had well-developed autonomic reflexes, whereas decerebrate dogs failed to show such reactions. A study of the literature of the past decade would seem to indicate that every aspect of autonomic activity is related in some way to the hypothalamus. Psychic disturbances, abnormal sleep, endocrine disorders, can all be produced by extirpation or stimulation of some part of this area. However, it becomes at once obvious that many authors would split up this portion of the diencephalon into a multitude of specific "centres," each subserving a specific function. Anatomical structure and small size would seem to suggest a fallacy in this multiple centre idea.

The next most reasonable hypothesis regarding hypothalamic function is that it is a dual mechanism, one part of which can activate the parasympathetic, the other, the ortho-sympathetic division of the autonomic nervous system. This would require afferent and efferent mechanisms and a reciprocal arrangement. The evidence obtained both by anatomical and physiological investigation would seem to bear this out.

In general, then, it can be securely stated that the anterior and middle nuclear groups described above are the "highest" proven centres of the parasympathetic outflow (although in the next few years we may find these, again, subservient to cortical centres), whereas the posterior group is the highest governing unit of the sympathetic division of the autonomic system.

Many ingenious experiments based upon stimulation or ablation of various hypothalamic areas have been carried out to prove this general and fundamental localization of autonomic representation. Objections, some of them quite justified, have been raised on the grounds

that stimulation may excite some tract passing through the area from still higher centres rather than a hypothalamic structure. But this has to some extent been overcome by the use of preparations in which one or both hemispheres have been removed before stimulation, thus allowing for degeneration of most of these itinerant fibres and obviating the difficulty of interpretation.

It is impractical, in an article of this nature, to cite more than a few references to the extensive amount of work which has been done on the experimental investigation of this region. Those interested in tracing the material to its fountain-head should consult Ingram's[5] excellent and up-to-date review.

The posterior nuclei—group C described above—seem to form a homogeneous system, the stimulation of which evokes a diffuse discharge from all divisions of the sympathetic system. These persist in chronic decorticate animals.

To Beattie[6, 7] and his co-workers we owe several ingenious experiments with regard to these nuclei. In one, the central end of the severed cervical sympathetic chain was anastomosed to the peripheral end of the cut hypoglossal nerve and time was allowed for regeneration. Then stimulation of the posterior hypothalamus resulted in the same type of muscular activity in the tongue of the animal as was exhibited on stimulation of the sympathetic trunk proximal to the anastomosis. Beattie has also shown that extrasystoles in the cat's heart induced by chloroform anaesthesia were abolished by section of the posterior hypothalamus. Experimental lesions involving the posterior hypothalamic nuclei were followed by descending degeneration into the spinal cord—partly into the formatio reticularis and partly into the intermedio-lateral columns of the thoracico-lumbar outflow. Lesions in this region, Beattie showed, caused lethargy and drowsiness, quiet and docile behaviour, hypothermia, glycosuria for a few days and pupillary constriction. Bilateral lesions are followed, in cats, by Horner's Syndrome, that well-known criterion of sympathetic paralysis.

Destruction of the mammillary bodies in cats and monkeys produces a state of catalepsy.

Stimulations of the tuber nuclei have given rise to responses reversed to those obtained from the posterior group—hyper motility of the gut, increased gastric tonus and gastric erosions (to be discussed below) have been obtained. It would seem, too, that in some cases the adiposogenital syndrome has arisen from destruction of these nuclei.

The anterior nuclei have become experimentally prominent recently due to their obvious connection with diabetes insipidus. This will be discussed later.

The above instances are only a few examples of the great mass of experimental data available on the hypothalamic nuclei, which, when pieced together, form a pretty logical picture of the hypothalamus as an autonomic integrator. But to get back to our concept of its role in the maintenance of homeostasis, to facilitate our understanding of this, it would be well to consider the reactions of the body to exposure to cold.

When the individual is exposed to cold of a rather severe degree, there first occurs shivering and increased muscular tone. Later, he is conscious of muscular relaxation and a feeling of warmth. He is, as Barcroft has put it, "basking in the cold." This stage is followed by a slowing up of his mental processes, unconsciousness and, finally, death. The whole process is an attempt to regulate heat loss and increase the body's heat production which at first succeeds. As conditions become worse, there is a gradual breakdown of the heat producing mechanisms and those preventing heat loss; the body temperature falls, the mental outlook changes, and death ensues.

Respiration is of fundamental importance in maintaining constant the internal environment, especially from the chemical standpoint. During exposure to cold, it is found that the inspiratory phase of the respiratory cycle becomes a series of short inspiratory efforts without any expiration between. Expiration is a sudden forcible act followed by another series of inspiratory efforts. Beattie[8] concludes that this is a heat conserving mechanism designed to permit the entry of only small amounts of cold air at a time and thus minimizing the heat loss of the body. He also concludes that the respiratory pattern during cold exposure is due to the activity of the hypothalamus, especially that part in relation to the thermosensitive zone. When shivering ceases, this apneustic type of breathing is replaced by the normal, meaning that the hypothalamus has ceased to inhibit the pneumotaxic centre either because the thermosensitive zone has lost its sensitivity owing to the fall in blood temperature, or because the hypothalamus itself is thrown out of action for the same reason.

Basal metabolism.—Exposure to cold causes an increased oxygen intake correlated with the rise in muscle tone. Under less extreme conditions oxygen consumption may not rise much due to reduction of heat loss from the skin by peripheral vaso-constriction without increased muscle tone. Early, too, there is a rise in blood sugar—carbohydrate oxidation being the main source of heat—which remains constant after shivering has been established. The early effects of cold exposure are due to the sympathetico-adrenal mechanism. Only when this is insufficient to combat heat loss do the muscles contribute—their increased tone being related to the hypothalamus. Stimulation of the hypothalamus[7] from the tuber region to the aqueduct of Sylvius produced a

rise in blood pressure, a rise in blood sugar, constriction of the peripheral vessels and apneustic breathing. Complete destruction of the posterior hypothalamus or section of the efferents therefrom result in a fall in body temperature.

Cardiovascular.—Early exposure to cold, resulting in increased sympathetico-adrenal activity causes an increase in the heart note of the human of from 20 - 30 beats per minute. During the phase preceding muscular activity there also occur the vaso-constriction and increased blood pressure alluded to above. None of these effects occur if the sympathetic is removed or the posterior hypothalamus is destroyed. Stavraky[9] showed that the pial vessels also became narrowed when the hypothalamus was stimulated.

Pilomotor activity—goose flesh—is a well-known cold reaction. Beattie, Brow and Long[7] obtained piloerection on posterior hypothalamic stimulation.

Water metabolism.—Cold induces a storage of blood in the liver and spleen and increases the flow of a urine low in chloride concentration. Together these result in the reduction of blood volume and a more concentrated serum. With regard to the urine, it has been suggested that tubular function is diminished while glomerular function remains. These reactions, designed to promote concentration of the blood to diminish heat loss by evaporation, do not occur in an animal poisoned with ergotoxin to the point of sympathetic paralysis or in one in which the infundibular region of the hypothalamus has been destroyed.[10]

Hence, from a consideration of the above, the maintenance of a constant internal temperature when that of the environment falls below that of the body depends on an intact posterior hypothalamus. The response to cold becomes interpretable as a series of closely coördinated reflexes, each of which may be perfect without the hypothalamus, but without it they cannot be coördinated to ensure a constant internal medium.

Limitations imposed by space prevent a consideration of the effects on the body of heat as detailed as those of cold, above. But a little should be said. Heat chiefly is lost from the skin and the lungs—by vaso-dilatation in the skin, producing heat loss by conduction, convection, radiation and evaporation of sweat. From the lungs, hyperpnea causes increased heat loss.

Bazett,[11] in a series of anterior decerebration experiments, concluded that animals had the capacity of reacting to cold and of regulating their own body temperature at a normal level in the absence of the corpus striatum and thalamus, and that the presence or absence of temperature control appeared associated with the preservation of the hypothalamus just cephalic to the mammillary bodies. Ranson and

Ingram[12] found that ablation of the rostral part of the lateral hypothalamus produced a post-operative rise in temperature, whereas the same procedure applied to the posterior part of the same area resulted in a prolonged loss of the animal's capacity to keep the body temperature up to normal. More recently, Magoun and his associates[13] have found that local heating of the brain of the cat with electrodes orientated by the Horsely-Clarke apparatus demonstrated a reactive region which responds to heat by respiratory acceleration, panting, and in some instances by sweating of the foot pads. The reactive elements were found concentrated in the medial portion of the caudal part of the ventral telencephalon and, in lesser concentration, extended back through the diencephalon to the anterior end of the mid-brain. In the diencephalon, they found that this area occupied the dorsal part of the hypothalamus and the ventral part of the thalamus.

These bits of evidence may seem somewhat contradictory, but at any rate we may conclude that the reactions of the body to heat, if not controlled, are at least, to a great degree, coördinated in the hypothalamic region.

Finally, Morgan and Vonderahae[14] have, by means of cell counts done on the hypothalamic nuclei of human subjects dead of heat stroke, advanced a working hypothesis of hypothalamic heat regulation. They have concluded that the larger cells of the more anteriorly situated paraventricular nucleus and tuber nucleus may be regarded as concerned with heat elimination, while the more posteriorly situated mammillary nuclei and probably the small cells of the paraventricular nuclei may be regarded as primarily concerned with the production and conservation of heat.

The Relationship of the Hypothalamus to the Hypophysis

The connections between the hypothalamus and the pituitary are nervous, vascular, and non-vascular. Briefly, the nervous connections are two. The supraoptico-hypophyseal tract from the supraoptic and paraventricular nuclei of the hypothalamic area passes down the pituitary stalk to the pars nervosa of the gland. The superior cervical sympathetic ganglion sends efferents along the ineternal carotid and its branches to the buccal derivates of the gland—the partes anterior, tuberalis and intermedia—these fibres being ultimately connected with the posterior hypothalamus.

The vascular connections are of the nature of a "portal" system described by Popa and Fielding[15] and Wislocki and King.[16] These workers have postulated that capillaries in the hypophysis unite into channels which again break up into capillaries in the hypothalamic region. But the balance of the evidence at the moment would seem to be against any direct vascular connection which could be of value in the transfer of secretion from the pituitary to the hypothalamic region.

Thirdly, we have the non-vascular "channels" in the form of well-defined spaces in the pituitary stalk. The colloid substance found in the pars nervosa and formed in the pars anterior may be seen travelling up this stalk. Its actual fate is unknown. Cushing believed that it was discharged into the third ventricle.

The hypothalamus controls the production and release of hormones from their respective endocrines. It also plays a part in determining the response of tissues and organs to these hormones, *viz.*, the resistance to insulin of diabetes of hypothalamic origin. Likewise, it probably responds to hormones. In many cases the retarding influence on the anterior pituitary by various endocrines is probably mediated by the hypothalamus.

Anatomy and development both would seem to indicate an intimate functional relationship between the hypothalamus and the pituitary. Many syndromes have been observed due to hypothalamico-hypophyseal dysfunction, but since the whole pituitary is controlled directly or indirectly by the hypothalamus it is practically impossible to tell (clinically) whether any function or lesion is purely hypothalamic or purely hypophyseal in origin. In an excellent survey, Lichtwitz[17] has enumerated thirteen "functions" and some forty "disturbances" attributable to hypothalamic, hypophyseal, or hypothalamico-pituitary disorder. It is impossible, due to the limitations of space, to consider these as I would wish, but the reader will find the material set forth in Lichtwitz's article.

It may be said, however, that four definite hypophyseal hormones are thought to be related either directly or indirectly to the hypothalamus. These are the melanophore-expanding, the antidiuretic, the diabetogenic, and the fat-metabolism hormone (see Beattie[8]). It would seem that lesions in either structure may cause manifestations attributable to deficiency or over-production of these hormones.

Sham Rage

This phenomenon, first recorded by Goltz[18] in 1892, really first awakened interest in the hypothalamus as a possible integrator of visceral function and a part of the mechanism of emotion. Philip Bard,[19] among others, has since enlarged on Goltz's observations and found, by making serial slices of the brain stem, that the well-known manifestations of massive sympathetic emotional discharge upon the slightest stimulus occurred in cats after ablation of the hemispheres, corpora striata and the cranial half of the diencephalon, *i.e.*, back as far as the posterior hypothalamus. He found that sham rage failed to develop after trans-secting the caudal extremity of the diencephalon or the cranial portion of the mesencephalon. He also excluded the thalamus

from participation in this activity. Sham rage is generally interpreted as a "release phenomenon," *i.e.*, removal of the "dampening" effect of the cortex over such sub-cortical activities as emotional excesses. It would seem related in some respects to various manifestations of mental disease.

Sleep

Fulton[20] suggests that sleep is essentially a parasympathetic integration. During normal sleep various divisions of the parasympathetic outflow are active; pupils are constricted, peristalsis proceeds, the heart is slowed, bodily oxidation is retarded, anabolism is dominant. Beattie, Brow and Long[7] found that the most striking feature of lesions in the region of the mammillary bodies was drowsiness and somnolence, and interpreted sleep as a damping down of hypothalamic activity. Hess[21] was able to induce sleep by faradic stimulation of the hypothalamic region of the brain stem. And so it would seem that normal sleep, together with its abnormal aberrations and variations, is linked closely to the hypothalamus, as we would expect from its parasympathetic manifestations.

Clinical Applications

Polyuria and Polydipsia.—Diabetes insipidus, with its excessive thirst, polyuria and emaciation, has long been regarded as due to disorder of the hypophyseo-hypothalamic "unit," but the role of each part of the "unit" in its production was long disputed. The work of Fisher, Ingram and Ranson[22] has definitely established that lesions in the supraoptic area, the supraoptico-hypophyseal tract, or the posterior pituitary may cause this syndrome. These three areas, then, constitute a neuroglandular unit effecting the production of the antidiuretic hormone controlling the function of diuresis. In some way, the tuber nuclei may be involved as Biggart[23] claims that lesions involving the tract running from the tuber nuclei to the mammillary bodies may render diabetes insipidus refractory to the antidiuretic hormone.

Glycosuria.—Two types of disturbances of sugar metabolism may follow hypothalamic lesions. These are glycosuria with and without hyperglycaemia. It is possible that in the latter cases the diabetic tendency may have been already present. According to Morgan[24] the paraventricular nucleus atrophies in diabetes mellitus. Lesions in the lateral portion of the tuber will prevent pancreatectomized dogs against the development of diabetes mellitus. Basal skull fractures with diencephalic injury are followed by the development of a temporary glycosuria. Likewise operations in these regions and parasellar neoplasms will cause deviations in carbohydrate metabolism.

Obesity and Cachexia.—It is becoming more and more obvious from clinical evidence that the hypothalamus has a more important influence on fat metabolism than the pituitary body.[25] Lesions in the

tuber region of rats have caused enormous obesity. In human pathology, in pre-adolescents, hypothalamic obesity is not accompanied by a cessation of growth, whereas pituitary obesity is. Pituitary and hypothalamic obesity are the same in distribution, *i.e.*, the fat is on the trunk and the proximal parts of the limb—a condition of lipodystrophia.

Sexual disorders.—Genital dystrophies are common to lesions of both the hypophysis and hypothalamus. Impotence, amenorrhoea or sexual retardation according to the sex and age of the patient may occur alone, or as is more often the case, in association with adiposity or cachexia, diabetes insipidus, hypersomnia, etc. Thus Fröhlich's syndrome may be either hypophyseal or hypothalamic in its origin. Bailey and Bremer[26] have definitely proven that these syndromes can occur as the result of hypothalamic injury alone. They caused lesions in the tuber cinereum by the lateral route, leaving the pituitary untouched (as verified histologically later), and as a result obtained in some cases a cachexia with genital atrophy and in others an insidiously developing adiposo-genital distrophy. Simmond's disease, once ascribed to hypophyseal atrophy, has been found with hypothalamic tumours and a normal pituitary.

Sleep disorders.—Narcolepsy and cataplexy are really merely exaggerations of normal reactions. Hypersomnia, insomnia, reversal of sleep rhythm and occasionally narcolepsy are often observed with encephalitis lethargica or as sequelae to this disease. Tumours of the posterior hypothalamus may give rise to states of hypersomnia with all the signs of normal physiological sleep. Hess' experiments, referred to above, were said to cause sleep by stimulation—hence it would appear that some focus exists in the hypothalamus, stimulation of which causes suppression of cortical activity. The mammillary bodies have been suspected because of their heavy projection to the thalamic nuclei.

Thermal dysregulation.—The relation of the hypothalamus to bodily and environmental temperature has been dealt with rather fully elsewhere in this paper. Hypothermia is most frequently seen combined with sleep disorders, adiposo-genital dystrophy and other signs of hypothalamic dysfunction. It is recognized as part of a syndrome of the posterior group of hypothalamic nuclei.

Vonderhae[27] and Davison and Selby[28] have presented interesting cases with varying combinations of the above clinical manifestations of hypothalamic disorder.

Ulceration of the Upper Alimentary Tract

Cushing[29] in his Balfour Lecture in 1931 revived Roitansky's theory of the neurogenic cause of peptic ulcer. He stated that experimental lesions, tumours or injuries anywhere in the course of tracts from the anterior hypothalamus to the vagal centre, presumably by parasympa-

thetic stimulation, are prone to cause gastric erosions, perforations and ulcers. Intraventricular pilocarpine or pituitrin, he found, caused an increase in gastric motility, hypertonicity, hypersecretion, retching and vomiting which ultimately contained occult blood. The interbrain has been shown to be the site of primitive emotions. However stimulated, direct stimulation of the tuber or of its descending tracts, or what amounts to the same thing, a release of the vagus from paralysis of the antagonistic sympathetic leads to hypersecretion, hyperchlorhydria, hypermotility, and hypertonicity, especially marked in the pyloric segment of the stomach. By the spasmodic contractions of the musculature, possibly supplemented by local vasospasm, small areas of ischaemia or haemorrhagic infarction are produced, leaving the overlying mucosa exposed to the digestive effects of its own hyperacid juices. The experimental work of Beattie,[30] and Hoff and Sheehan,[31] bears this out and neurogenic factors have since been included as playing a great part in the causation of some if not all peptic ulcers.

The Hypothalamus and Emotions

A real interest in the relationship between the hypothalamus and emotion has recently become manifest. Sham rage is a good example of this relationship. Uncontrolled emotional manifestations are often observed in encephalitis, pseudo-bulbar paralysis, disseminated sclerosis, etc., and the placidity of chronic hydrocephalics is characteristic. We are all familiar, too, with subjective feelings associated with emotional reactions—the palpitation that comes with a sudden shock, the feeling of nausea that may follow narrow escape from an accident, "cold sweat," and many others.

At the present time psychoanalysts are busy studying the possible psychogenesis of peptic ulcer, mucous colitis, spastic bowel, hypertension, bronchial asthma, eczema, diabetes mellitus, arthritis, migraine and a host of other conditions.

In conclusion, it might be well to recall Cushing's words to the effect that "there has been a tendency to overload the hypothalamus with functional responsibilities and to seek in its disorders the solution of too many of our unsolved problems." And it may be that Hughlings Jackson's well-established principle that the localization of a lesion does not necessarily mean the localization of a fuction, has often been forgotten. But generally speaking, the available physiological and clinical evidence points to two distinct mechanisms in the hypothalamus; one in the posterior portion designed to produce coördinated responses of the numerous sympathetic reflexes, the other in the anterior portion acting a like role for the parasympathetic system. Each set seems directed toward the maintenance of a constant internal melieu, and there is some evidence that when one acts, the other is inhibited. The hypophysis

is a part of this dual mechanism, partly controlled and partly controlling. And we might best sum up with the words of Beattie, "The whole of this autonomic nervous system has one essential function—the maintenance of an internal environment within those normal limits within which bodily and mental activities reach their highest efficiency."

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Abstracts

URINARY TRACT INFECTIONS, COMPARISON OF MANDELIC ACID, ETC.

By E. N. Cook and E. B. Sutton

J. Urol., v. 42, p. 880, November, 1939

The treatment of such infections of the urinary tract as are amenable to drugs may profit greatly by the advances that have been made recently in the development of new therapeutic agents, but the maximum benefit can be obtained in these cases only when the nature of the causative organism is accurately determined. This knowledge permits a much more effective choice of the therapeutic agent. The reaction of the medium in which the agent must act is another item of great importance, and should be known all through the course of treatment. In general, all Gram-negative bacilli may be destroyed with mandelic acid or sulphanilamide. Though mandelic acid may be more difficult of administration, preliminary reduction in dosage and variation of the mode of giving the drug in pill or liquid form usually permits its adequate administration. This drug may be used with much less danger of untoward reaction than sulphanilamide, if renal function is normal.

JAUNDICE. USE OF VITAMIN K IN TREATMENT OF HÆMORRHAGIC DIATHESIS

By S. R. Townsend and E. S. Mills

Can. Med. Assoc. J., v. 41, p. 111, August, 1939

Bringing additional data as to the efficacy of vitamin K in preventing hæmorrhage in operations on jaundiced patients, the present paper reports 10 cases of obstructive jaundice treated with vitamin K and bile salts. All of these patients showed a delayed clotting time at first, but in nine of them the clotting time returned to normal after administration of vitamin K and bile salts. There are certain jaundiced patients who do not show any prolongation of clotting time pre-operatively, but the authors believe that they should be given the vitamin treatment regardless, since loss of blood during the operation may sufficiently lower the prothrombin level to place the patient in danger of hæmorrhage. One of the causes for the lack of vitamin K in patients with biliary tract disease may well be the low-fat diet which is almost routinely prescribed for such patients for extended periods before they finally come for operative procedure.

PNEUMONIA, DEVELOPMENT OF TOLERANCE TO SULPHAPYRIDINE BY COCCI

By R. W. Ross

Lancet, v. 1, p. 1207, May 27, 1939

There has been some suspicion in the past that strains of pneumococci which originally were adversely affected by the presence of sulphapyridine might, if grown for some time in contact with sublethal amounts of the drug, subsequently develop resistance or "fastness" to it. A case of pneumococcal meningitis gave an opportunity to test out this theory. Cultures made from the spinal fluid of the patient early in the illness yielded a strain of pneumococcus which was adversely affected by sulphapyridine *in vitro;* at this stage of the disease, the administration of sulphapyridine to the patient brought about clinical improvement of the meningitis. Later, however, adequate doses of the drug seemed to have little beneficial effect, and the patient finally succumbed to the infection. Cultures taken from the spinal fluid at autopsy yielded a pneumococcus much more resistant to sulphapyridine when tested in the laboratory.

DIGESTION, IMPORTANCE OF BILE IN ABSORPTION OF VITAMINS

By H. R. BUTT

American Journal Dig. Dis., v. 6, p. 127, April, 1939

It is well known that very little fat can be absorbed from the intestinal tract if bile is excluded from it. The close relationship of the fat-soluble vitamins to the sterols renders it probable that bile also takes part in the absorption of these elements. Evidence for this belief has been presented by Greaves and Schmidt in the case of vitamins A and E; deoxycholic acid is believed to be the constituent of bile which enters into the reaction most intimately. The importance of bile has recently been emphasized by the discovery of the part it plays in the absorption of vitamin K. When bile is excluded from the alimentary tract in certain animals, the lack of absorption of this vitamin becomes so marked that the prothrombin content of the blood falls to low levels, and a hæmorrhagic diathesis appears. These phenomena can be corrected by the oral administration of vitamin K concentrates with bile salts.

TRANSFUSION: EFFECT OF SULPHANILAMIDE ON BLOOD TYPING

By G. A. SCOTT and O. MEERAPFEL

Lancet, v. 2, p. 244, July 29, 1939

Since the majority of severe reactions following blood transfusions may be traced to errors in typing and cross-matching, any factor which is capable of falsifying such tests is of great importance. Patients with severe infections of certain types are frequently treated with heavy doses of sulphanilamide, and they often require in addition one or more blood transfusions to combat the anæmia which frequently accompanies infection. The authors observed two cases in which treatment with heavy doses of sulphanilamide or dimethyl disulphanilamide was followed by an alteration in the agglutinating power of the serum for the blood cells of donors. The serum of these two patients was found to agglutinate the cells of donors belonging to all four blood types. Sulphanilamide was added *in vitro* to normal serum and stood four days. At the end of this time, the serum agglutinated red cells of the blood group to which it originally belonged. Smaller doses did not have this action.

PELLAGRA, SUBCLINICAL FORMS, PREVALENCE IN CHICAGO

By V. L. EVANS

Illinois Medical Journal, v. 76, p. 458, November, 1939

Pellagra is not believed to be a common disease in Chicago, and therefore special interest attaches to this report from a private sanitarium in the vicinity of that city. Out of 205 cases of nervous and mental diseases admitted to the institution in 1938, 13 were diagnosed as pellagra. Before the advent of nicotinic acid therapy the author had noticed many patients with stomatitis and glossitis which could not be adequately accounted for on any basis then known. Some of these patients were treated with yeast, but the results were slow and doubtful. In 1938, however, a better background for the understanding of unexplained stomatitis and glossitis was available, and nicotinic acid was widely available, and the 13 patients were treated with this drug. The oral lesions responded well, and two patients were relieved of their mental symptoms. The other eleven had psychoses which were not caused by pellagra. Their mental conditions were not improved by the medication.

INCREASED NEED FOR VITAMIN C MEASURED IN FEVER

By FALKE

Klin. Wchnschr., v. 18, p. 818, June 10, 1939

To determine the amount of vitamin C used up during the course of fevers, the concentration of ascorbic acid in the blood was measured during febrile episodes, and the amount of pure ascorbic acid which had to be given during this period to prevent a fall in the blood level was estimated. Fifteen patients were studied during a total of 58 days of fever, and the vitamin C requirements were compared with those of 72 fever-free days in the same patients. It was found that approximately 100 milligrammes more of vitamin C were re-

quired daily in the presence of fever than in its absence. If no supplementary ascorbic acid was given during febrile periods, a fall in vitamin C excretion took place; in order to prevent this fall, approximately 300 milligrammes of ascorbic acid had to be given daily to each patient. The calculations were complicated by the fact that the amount of ascorbic acid which was metabolized was dependent partially on the amount of the supplement which was given.

PREVENTION OF MOTOR PARALYSIS IN SPINAL ANÆSTHESIA

By H. KOSTER, A. SHAPIRO, R. WARSHAW and M. HARGOLICK

Arch. Surg., v. 39, p. 682, October, 1939

The authors were interested in developing a procedure which would lessen the duration of motor paralysis in the lower extremities which follows the use of procaine for spinal anæsthesia. It was found that at the time procaine is injected into the subarachnoid space another needle may be inserted into this space three interspaces above the first needle. Spinal fluid may be drained out through this second needle, and will be found to contain a fraction of the procaine. Three to five successive 10-cc. portions of normal saline solution can then be injected through the first needle to wash out more of the procaine. By no means can all of the procaine be removed by this procedure, but if the withdrawal and washing are begun immediately after the injection motor paralysis fails to develop, even though anæsthesia is obtained. If the washing out procedure is delayed motor paralysis nevertheless has a much shorter duration. Withdrawal of fluid alone was found less effective.

VAGINITIS, GONOCOCCAL, TREATMENT WITH ESTROGENS

By A. JACOBY, D. E. MADONIA, S. M. TILL and T. H. WOOD

American Journal Obst. and Gynec., v. 38, p. 140, July, 1939

To evaluate the estrogenic treatment of gonococcal vaginitis, a study was undertaken at a large clinic in New York. One hundred patients, varying in age from 3 weeks to 14 years, were treated with vaginal suppositories containing 1,000 International Units of estrogen. One suppository was placed in the vagina each night. Of the 100, 92 patients appeared to be cured after a period of treatment lasting from 14 to 435 days. However, 24 of these patients relapsed in an average time of 109 days after being apparently cured. Sixteen patients were never cured by this treatment. This leaves 68 patients apparently permanently cured as far as the authors' observations extended. Several widely-repeated axioms concerning estrogenic treatment are called into question, *e.g.*, the gonococci were found abundantly in very acid secretions at times; the theory that estrogens act by increasing the layers of the stratified vaginal epithelium fails to take cervical infection into account.

DIAGNOSIS AND TREATMENT OF VITAMIN B_1 DEFICIENCY

By N. JOLLIFFE

Bulletin New York Acad. Med., v. 15, p. 469, July, 1939

The most definite signs and symptoms of vitamin B_1 deficiency are anorexia, fatigue and a neurological and circulatory syndrome. Peripheral neuritis involving a single nerve, not bilateral and not involving first and predominantly the lower extremities, is probably not due to vitamin B_1 deficiency alone. Deficiency should be suspected in the indigent, in persons with eccentric dietary habits, alcohol addicts and patients with diseases which increase metabolism or decrease intestinal absorption. The treatment includes rest, diet, vitamin B_1 and correction of factors responsible for the deficiency wherever this is possible. The diet should be supplemented by 50,000 I.U. of vitamin A, 400 to 500 mg. of vitamin C, and a rich source of the vitamin B complex. Thiamin chloride should be administered parenterally in large doses — amounts up to 1,000 mg. in the first 24 hours in severe cases—and these should be continued until saturation is obtained. This can be detected by a distinct odour, which resembles burnt rubber, in the urine.

Editorial

With this issue of the Journal, Volume ten is completed. The Editor wishes to take this opportunity of thanking all who have kindly aided in its production.

On several occasions we have attempted to point out to the student body the value of publishing in the Journal and the increase in the number of student articles received, we hope, is an indication that we have succeeded. The work necessary to make the publication possible is well repaid by the remarks of appreciation that are so often made. The Journal has benefited a great deal by criticism, which has always been well meant and has been received as good advice.

As to the future of the Journal, we may rest assured. Improvements will be made just as long as a co-operative student body exists at Western.

J. D. ATCHESON.

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AN APPRECIATION *

As I review in my thoughts the medical graduates of our University I am not unmindful of the men I have known personally and by reputation, some of whom are famous because of their accomplishments in the field of medical research and others for their outstanding contribution in some specialized work. But I think particularly of the many eminent doctors and family physicians who are serving the public as general practitioners located in remote districts of our land on the very periphery of so-called civilization, and who are making their contribution to social and scientific advancement, quite "unhonoured and unsung." On occasion I have visited the rural doctors—rugged, honest, big-hearted men, many of them sustaining in quiet fortitude the pioneer conditions under which they live and work. I have watched them as they used their *hands* and *brains*—no expensive diagnostic and therapeutic aids—no instruments of precision—no staff of assistants and no voluminous libraries. To these men great credit is due; *yes*, overdue. Their financial rewards are not often in evidence but reward comes in results honestly achieved and in the fine appreciation by those whom they have served so faithfully. Maybe in the hereafter these unselfish contributors to the welfare of the people will sit in the seats of the Blessed, and it will be said of them:

"My forebears back to Adam's line,
When *I* arrive,
Will shout and cheer and whisper in their neighbour's ear:
'We're relatives of *his'*."

*W. H. McGuffin, M.D., Calgary, Alta. Diamond Jubilee Banquet, Oct. 14, 1938.